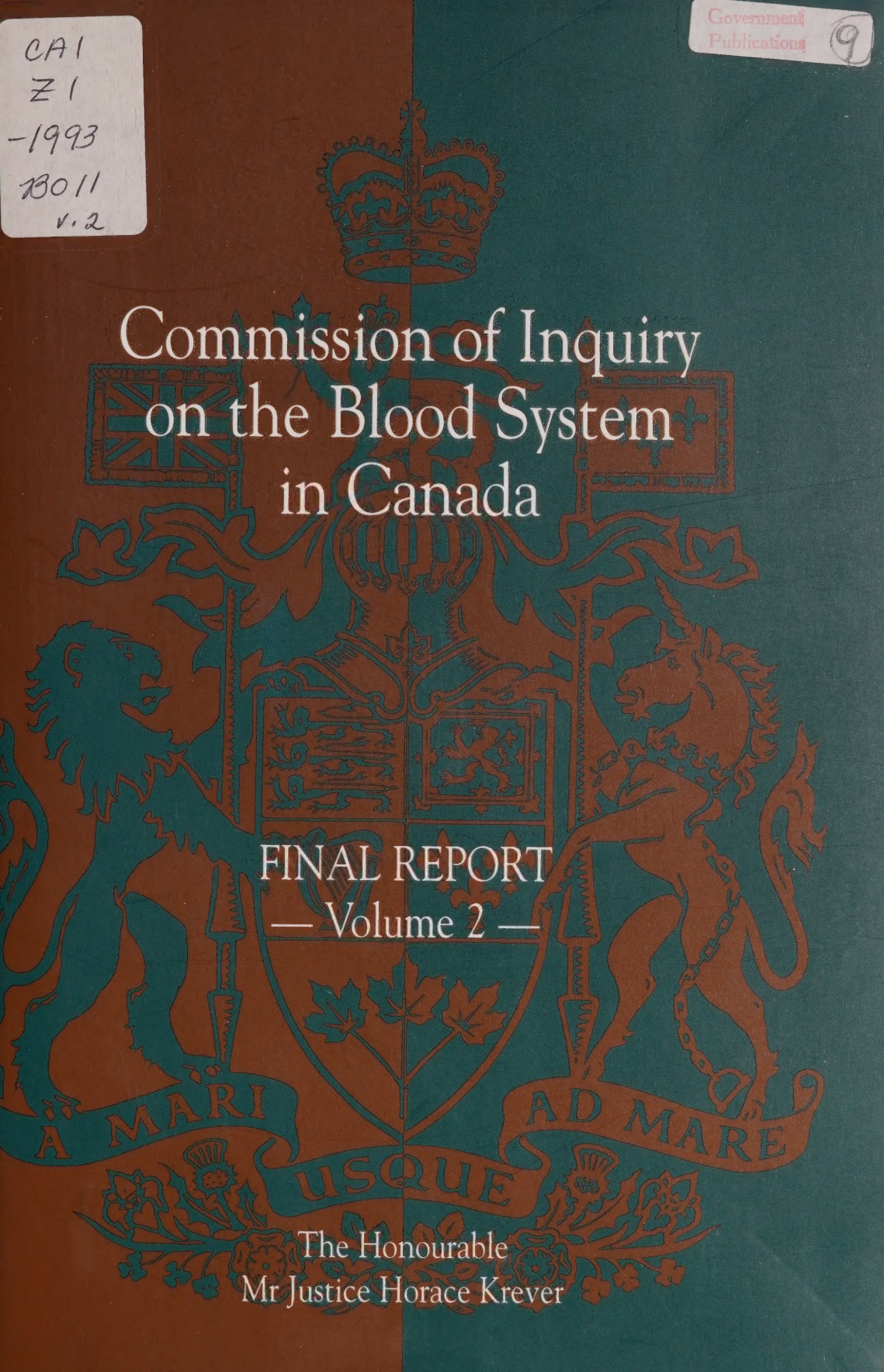


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Commission of Inquiry on the Blood System in Canada

FINAL REPORT
— Volume 2 —

The Honourable
Mr Justice Horace Krever

Commission of Inquiry
on the Blood System
in Canada



This Final Report consists of three volumes. The table of contents in each volume is complete for that volume and abbreviated for the other two volumes.

Commission of Inquiry on the Blood System in Canada

FINAL REPORT
— Volume 2 —

The Honourable
Mr Justice Horace Krever

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The Risk in Factor Concentrates

Hemophiliacs in the United States began to use factor concentrates in the late 1960s and early 1970s. It is now known that some U.S. hemophiliacs who used concentrates were infected with the human immunodeficiency virus (HIV), the causative agent of AIDS, as early as 1978. The Canadian Red Cross Society (Red Cross) began to distribute factor IX concentrate in 1976 and factor VIII concentrate in 1979. The infusion of the concentrates by Canadian hemophiliacs became common only after the Red Cross began to distribute them as part of its national program. Some Canadian hemophiliacs might have been infected with HIV as early as 1978, and some certainly were infected soon thereafter. In the summer of 1982, some U.S. hemophiliacs were found to have the symptoms of AIDS, and concern was focused on the only element they had in common – that they had used factor concentrates. In the summer of 1985, the Red Cross began distributing concentrates that had been heat treated to inactivate viruses, thus reducing the risk of transmitting AIDS. The non-heat-treated concentrates that were distributed in Canada during the first half of 1985 were made from donations of whole blood and plasma collected during 1984. This chapter is concerned primarily with events from the summer of 1982, when the first U.S. hemophiliacs were found to have the symptoms of AIDS, to the end of 1984, when the last plasma that was used to make non-heat-treated concentrates was collected. It includes a review of the ways in which blood and plasma were collected; the processes by which factor concentrates were made; and the measures that were taken, before the introduction of heat-treated concentrates in Canada, to reduce the risk that the use of concentrates would cause AIDS.

The risks inherent in the manufacture of factor concentrates

Plasma is the liquid component of blood that can be separated from the cellular components, including the red blood cells and the platelets. There are two ways to obtain plasma. “Source plasma” is collected by plasmapheresis, a process by which only the plasma is collected. “Recovered plasma” is made by separating the plasma in a donation of whole blood from the other components. In the United States in the late 1970s and early 1980s, source

plasma could be collected from a person a maximum of fifty-two times a year; whole blood could be collected six times a year. In Canada, source plasma could be collected approximately twenty-five times a year; whole blood could be collected four times a year.

Factor concentrates are made from plasma. Factor VIII concentrate must be made from plasma that is frozen soon after it is collected; otherwise the factor VIII proteins the plasma contains will lose activity and the concentrate will be ineffective. Some of the factor VIII concentrates distributed by the Red Cross were made from fresh frozen source plasma and recovered plasma that had been collected in the United States. These concentrates were bought by the Red Cross from U.S. and Canadian fractionators, and in this Report they are described as "commercial" products. The other factor VIII concentrates distributed by the Red Cross were manufactured by fractionators from fresh frozen recovered plasma and source plasma collected by the Red Cross. These concentrates are called "custom-fractionated" products. Factor IX is more stable than factor VIII and, as a result, factor IX concentrate can be manufactured from plasma that has not been fresh frozen. The Red Cross distributed commercial and custom-fractionated factor IX concentrate for some years, but by 1981 all factor IX concentrate distributed in Canada was made from Canadian plasma.

Factor concentrates were manufactured in large-scale processes that involved the pooling of plasma from thousands of donors. The entire pool could be contaminated by a single unit from a donor who was infected with HIV.

In the absence of a direct test for the causative agent of AIDS, there were four measures that could be taken to reduce the risk of infection from non-heat-treated factor concentrates. The first was to introduce measures to prevent persons at high risk of contracting AIDS from donating whole blood and plasma. The second was to use an indirect, or surrogate, test to detect donations that might be infective. The third was to design processing procedures that would minimize the risk of contamination of the concentrates. The fourth was to minimize risk in the treatment of hemophiliacs, one important element of which was the information given to hemophiliacs and their physicians about the risks in using concentrates. All four approaches are reviewed in this chapter. Because the Red Cross distributed some concentrates that were made from U.S. plasma and others that were made from Canadian plasma, the measures that were taken in both countries to reduce the risk of contamination affected the health of Canadians.

Two variables determine the risk that a batch or lot of concentrate might be contaminated by a unit of plasma that comes from a person infected with a disease-causing pathogen. They are the number of donors whose plasma is pooled for processing, and the prevalence of infection in the population of donors from whom the plasma is collected. There is a simple binomial equation that relates the two variables to the risk. It is a standard equation that was known and used at least as early as 1980, and as late as 1996, to calculate

the risks associated with concentrates. In 1980, *Vox Sanguinis*, the journal of the International Society of Blood Transfusion, published a series of short articles by eight persons who were experts in blood banking and blood products under the title "What Is the Importance of the 'Small Pool Concept' in the Preparation of Fraction I and Cryoprecipitates for the Prevention of Post-transfusion Hepatitis?" In one of the articles, the equation is used to calculate the risk of hepatitis in factor concentrates. In 1996, the journal *Transfusion* published an article by five senior employees of the Office of Blood Research and Review, U.S. Food and Drug Administration, entitled "Considerations of Pool Size in the Manufacture of Plasma Derivatives." In the article, the same equation is used to calculate the risk of concentrates being contaminated with a disease-causing organism.

Table 14.1 contains the results of calculations using the equation. It is apparent from the results that, when concentrates are made from large pools of plasma, there is a significant probability that the pools will be contaminated, even when the prevalence of infection among donors is low. The "risk in concentrates" that is discussed in this chapter is the probability that they have been made from a pool containing at least one unit of plasma from an infected donor. The table allows a ready comparison of the prevalence of infection in the donors and the inherent risk in the concentrates.

Table 14.1
Probability that a plasma pool contains plasma contributed
by one or more infected donors, as a function of the prevalence
of infection in the population of donors and the number
of donors contributing plasma to the pool (per cent)

Prevalence of infection among donors	Number of donors contributing to the pool						
	2,000	5,000	7,5000	10,000	20,000	50,000	100,000
1:5,000	33	63	78	86	98	100	100
1:10,000	18	39	53	63	86	99	100
1:20,000	10	22	31	39	63	92	100
1:50,000	4	10	14	18	33	63	86
1:100,000	2	5	7	10	18	39	63
1:200,000	1	2	4	5	10	22	39
1:500,000	0	1	1.5	2	4	10	18

Risk calculated using the standard formula for the operation: probability that a pool contains plasma from one or more infected donors = $1 - (1 - p)^n$, where p = the prevalence of infection among donors and n = the number of contributors to the plasma pool.

The possibility that a few persons infected with the agent causing AIDS could contaminate huge amounts of concentrate was recognized even before the agent was identified. In July 1983, Dr Michael Rodell, the vice-president (regulatory and technical affairs) of the Armour Pharmaceutical Company (Armour), one of the four U.S. fractionators, described the possibility of large-scale contamination at a meeting of the blood products advisory committee of the Center for Biologics Evaluation and Research, a standing committee that advised the U.S. Secretary of Health, the assistant secretary of health, and the commissioner of the Food and Drug Administration. Dr Rodell said that, on average, persons who were paid for their plasma had it collected forty to sixty times per year. He then estimated that, at that rate, and given the pool sizes used in the United States, four infected persons could contaminate the entire world supply of factor VIII concentrate. Dr Rodell's conclusion was based on an analysis that was confined to concentrates made from U.S. plasma. Those concentrates were exported to many countries, including Canada. Dr John Derrick, the internal adviser on regulatory affairs and good manufacturing practices for the Red Cross's blood transfusion service, attended the meeting at which Dr Rodell spoke and recorded his statement.

U.S. plasma

The U.S. fractionators used both source and recovered plasma in the manufacture of commercial blood products, including factor VIII and factor IX concentrates. Almost all the source plasma came from persons who were paid for their plasma. Almost all the recovered plasma came from volunteers.

The centres collecting source plasma were operated by several kinds of organizations during the period under review. Much of the source plasma was collected for their own use by the four U.S. fractionators, each of which operated many centres. Much was also collected by approximately twenty-five other corporations that operated two or more centres; most of the plasma collected by them was sold directly to the fractionators through long-term contracts, but some was sold to them through plasma brokers. A smaller, but significant, amount was collected by other corporations that operated only one centre; they sold most of their plasma to the fractionators through brokers. A small amount of the source plasma was collected by not-for-profit organizations. The number of centres in each of these sectors is shown in Table 14.2. During 1982–4, their collective operations each year yielded more than 4 million litres of source plasma from more than 6 million individual plasmapheresis collections.

Whole blood was collected in three kinds of centres in the United States. The American Red Cross's centres collected approximately 50 per cent of the total; community blood centres, approximately 40 per cent; and hospital blood banks, the remainder. The American Red Cross did not sell the recovered plasma from its donations to the fractionators; instead, it had them custom-fractionate the plasma – approximately 900,000 litres per year, recovered

Table 14.2
Number of centres collecting source plasma in the United States

	1979	1980	1981	1984
Operated by fractionators	121	123	107	92
Owned by multicentre corporations	171	167	213	177
Owned by single-centre corporations	96	104	50	48
Operated by not-for-profit organizations	9	9	11	19
Total	397	403	381	336

Source: U.S. Office of Technical Assessment, "Blood Policy and Technology" (Washington, 1985)

from more than 4 million whole-blood donations – and then sold the finished blood products. The community blood centres and the hospital blood banks each year sold approximately 500,000 litres, recovered from more than 2 million whole-blood donations, to the fractionators, usually through brokers.

Most hospital blood banks did not require licences from the U.S. Food and Drug Administration because they were not normally engaged in interstate commerce except in one respect – the sale of recovered plasma to the fractionators. Hundreds of blood banks sold recovered plasma, often shipping it across state lines, and it would have been difficult for the Food and Drug Administration to license and inspect all of them. Accordingly, the blood banks and the fractionators were allowed to enter into "short supply agreements," under which the fractionators were required to ensure that the suppliers of their plasma complied with the Food and Drug Administration's regulations and standards.

U.S. efforts to reduce the number of contaminated plasma units

During 1981–2, the number of AIDS cases in the United States reported to the Centers for Disease Control in Atlanta grew at an alarming rate. The vast majority of the reported cases were of homosexual men and intravenous drug abusers. During 1982, cases of AIDS transmitted through the use of blood and blood products began to be reported.

The U.S. blood and plasma centres regularly collected from two groups of persons who were at high risk of contracting AIDS: homosexual men and prison inmates. Plasma was collected at centres, licensed by the Food and Drug Administration, in prisons in Arkansas, Florida, Louisiana, and Mississippi.

By way of contrast, because of the high prevalence of hepatitis B in prisons, the Canadian Red Cross Society had stopped collecting donations from prison inmates in 1971.

On 2 October 1982, the medical and scientific advisory council of the U.S. National Hemophilia Foundation met and passed a series of resolutions that were later endorsed by the foundation. The council recommended that plasma not be collected from "homosexuals, intravenous drug abusers, and those who have recently resided in Haiti" because those groups had "a relatively high incidence of AIDS" and "AIDS may be transmitted by blood products." It also recommended that plasma obtained from whole-blood donations not be used to make factor VIII concentrate unless the blood centres it came from were refusing donations from members of those high-risk groups.

On 13 December 1982, Dr Dennis Donohue, the director of the Office of Biologics of the Food and Drug Administration, the federal agency regulating the blood system in the United States, met informally with representatives of the four U.S. fractionators. He asked them not to use plasma collected by plasmapheresis in high-risk areas (which he identified as New York, San Francisco, and the Hollywood area of Los Angeles), not to use plasma collected in prisons, and not to use plasma recovered from blood donations collected in high-risk areas (especially donations collected by the Irwin Memorial Blood Bank, the community blood centre in San Francisco). All four fractionators complied with his request.

The Alpha Therapeutic Corporation (Alpha) was the first fractionator to institute a program to exclude members of high-risk groups. On 20 December 1982, it instructed all its plasma collectors to ask prospective donors whether they were intravenous drug users or homosexuals and whether they had resided in Haiti. In the first three weeks of the program, 308 persons were excluded because they identified themselves as being in one of the high-risk categories, and an even larger number of persons excluded themselves without stating a reason. Alpha also told hemophilia treatment centres, in a memorandum dated 22 December 1982, that it did not use plasma collected from prison inmates because prisoners were recognized as a high-risk population.

On 21 December 1982, the National Hemophilia Foundation issued a medical bulletin. It read, in part:

There is an increased concern that AIDS may be transmitted through blood products. Patients and parents should be aware of the potential risks. There is no conclusive evidence that cryoprecipitate or fresh frozen plasma will reduce the risk of AIDS. We feel, however, that this is no time to introduce concentrates to patients who have never used them before, except when there is an overriding medical indication. Examples of patients who have not [been], and therefore should not be, introduced to concentrates at this time are as follows: newborn infants (through age 4); newly diagnosed cases of hemophilia; and those with mild disease. At this time

the NHF [National Hemophilia Foundation] AIDS Task Force does not recommend a change in therapy. And, by all means, one should not withhold the use of clotting factor therapy when needed.

Cryoprecipitate and fresh frozen plasma were blood components that, unlike factor concentrates, were not made from large pools of plasma.

On 4 January 1983, a public meeting, convened by the Centers for Disease Control, was held to discuss AIDS and the U.S. blood system. Representatives of the National Institutes of Health and the Food and Drug Administration attended the meeting. The U.S. blood centres were represented by the American Association of Blood Banks, the American Red Cross, and the Council of Community Blood Centers. The U.S. plasma centres were represented by the American Blood Resources Association. Although they were members of the American Blood Resources Association, all four U.S. fractionators – Alpha, Armour, the Cutter Biological Division of Miles Laboratories Inc. (Cutter), and the Hyland Therapeutics Division of Travenol Laboratories Inc. (Hyland) – also sent representatives. There was agreement that “it would be desirable to exclude high-risk donors to reduce the risk of AIDS transmission,” but no consensus was reached at the meeting on how this should be accomplished.

On 13 January 1983, the American Association of Blood Banks, the American Red Cross, and the Council of Community Blood Centers issued a joint statement announcing measures that should be taken by blood centres to reduce the risk of AIDS. They recommended that donors be asked specific questions to determine whether they had any symptoms of AIDS or exposure to someone with AIDS: “In particular, all donors should be asked questions designed to elicit a history of night sweats, unexplained fevers, unexpected weight loss, lymphadenopathy [swelling of the lymph nodes], Kaposi’s sarcoma. All positive or suggestive answers should be evaluated before anyone donates.” They said expressly that “[d]irect or indirect questions about a donor’s sexual preference are inappropriate.”

In 1983, there was no laboratory test for the virus that causes AIDS. At the meeting on 4 January convened by the Centers for Disease Control, the participants discussed the use of a surrogate test to identify persons at high risk of contracting AIDS. A surrogate test is an indirect way of identifying the likelihood of infection with a particular disease that cannot be identified directly. One form of surrogate test uses the marker of another disease that has come to be associated with the disease in question, because they are both found in the same population. In this instance it was proposed that blood and plasma units be tested for anti-HBc, the antibody to the core of the hepatitis B virus. The presence of that antibody in a person’s blood indicates a current or previous infection with hepatitis B. Because, in one study, 90 per cent of persons reported to have AIDS also tested positive for anti-HBc, a positive test for the antibody was considered a significant indication of possible

infection with AIDS. The prevalence of hepatitis B was known to be high among both prisoners and homosexual men. It was high among prisoners because it was transmitted by sharing needles to inject drugs. It was high in both groups because it was transmitted by sexual contact. As with all other measures discussed at the 4 January meeting, no consensus was achieved with respect to the use of surrogate testing. The representative of the New York Blood Center did, however, propose that a pilot study of the surrogate test be undertaken to determine its effectiveness in identifying persons in the high-risk groups, its cost, and its impact on the blood supply. The joint statement issued on 13 January did not recommend surrogate testing:

While there is no specific test for AIDS, there are laboratory and clinical findings that are present for nearly all AIDS patients. The use of these non-specific markers, for example ... anti-HBc, [is] being evaluated in those areas of the country where AIDS is prevalent. We do not advise routine implementation of any laboratory screening program for AIDS by blood banks at this time.

On 14 January, the medical and scientific advisory council of the National Hemophilia Foundation made recommendations to the manufacturers of factor VIII concentrate and to blood centres. The recommendations to the manufacturers read as follows:

- A. Serious efforts should be made to exclude donors that might transmit AIDS. These should include:
 1. Identification, by direct questioning, [of] individuals who belong to groups at high risk of transmitting AIDS, specifically male homosexuals; intravenous drug users; and those who have recently resided in Haiti.
 2. Evaluation and implementation (if verified) of surrogate laboratory tests that would identify individuals at high risk of AIDS.
 3. In addition, the manufacturers should cease using plasma obtained from donor centers that draw from population groups in which there is a significant AIDS incidence. It is clear from the epidemiologic data that the pool of individuals at risk for AIDS transmission is not uniform throughout the country and that a great deal could be achieved by excluding donors from the "hot spots."
- B. Efforts should be continued to expedite the development of processing methods that will inactivate viruses potentially present in factor VIII concentrates.
- C. There should be an evaluation of the possibility that the yield of factor VIII in pheresis donors could be increased using DDAVP [deamino-8-D-arginine vasopressin, a synthetic analogue of the human

hormone vasopressin that increases the level of factor VIII in circulation] or exercise to maximize yield. This would permit a reduction in the size of the donor pool and would compensate for losses in plasma that might occur due to the steps noted above.

- D. There should be an evaluation of the feasibility of fractionating and processing plasma so that lyophilized small pool products are available. While this will certainly be more costly, it may be the only way to break out of the present dilemma without going to an all-cryoprecipitate effort.
- E. Concentrate manufacturers should immediately cease purchase of recovered plasma for factor VIII concentrate from blood centers that do not meet the criteria listed in A above. These criteria should also apply to the production of cryoprecipitate.
- F. Manufacturers should accelerate efforts towards the production of coagulation factor concentrates by recombinant DNA technology.

The recommendations to the blood centres were related to increasing the amount of cryoprecipitate available for the treatment of hemophiliacs in place of factor VIII concentrate.

On 28 January 1983, the American Blood Resources Association made a number of recommendations to its members, which included the fractionators and other corporations that operated plasmapheresis centres. It recommended that plasma centres prepare pamphlets about AIDS that contained statements intended to discourage high-risk persons from donating plasma, that prospective donors be required to read the information about AIDS and acknowledge that they were not members of the high-risk groups identified, that plasma not be collected from members of the high-risk groups, that persons working in plasma centres be told about AIDS and its symptoms, that prospective donors be asked whether they had any of the symptoms of AIDS, and that plasma not be collected from persons with the symptoms of AIDS. The association recommended that the same measures be taken by centres collecting whole blood from voluntary donors, because every year several million units of plasma recovered from whole-blood donations were used by fractionators to make factor concentrates.

On 4 March 1983, a set of interim guidelines that had been developed by the Public Health Service were issued. It recommended that the centres tell persons from whom they collected blood or plasma that members of high-risk groups (defined as persons with AIDS, sexual partners of persons with AIDS, persons with the symptoms of AIDS, sexually active homosexual or bisexual men with multiple sexual partners, Haitians, present and past intravenous drug users, and the sexual partners of any of these persons) should refrain from giving blood or plasma. It also said that studies should be conducted to evaluate laboratory tests.

On 24 March, the Food and Drug Administration issued three sets of guidelines – for blood centres, for plasma centres, and for manufacturers of plasma derivatives – that replaced the interim guidelines. For the blood centres, the administration recommended:

Educational programs should be instituted to inform persons at increased risk of AIDS that until the AIDS problem is resolved or definitive tests become available, they should refrain from blood donation because of the potential risk to recipients of their blood. As presently defined this group includes: persons with symptoms and signs suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners, Haitian entrants to the United States, present or past abusers of intravenous drugs, and sexual partners of individuals at increased risk of AIDS ...

Re-education of personnel responsible for donor screening should be conducted with special attention to recognition of the early signs and symptoms of AIDS. The donor medical history should include specific questions designed to detect possible AIDS symptoms or exposure to patients with AIDS. Standard operating procedures (SOP) should be revised to include questions which elicit a history of night sweats, unexplained fevers, unexpected weight loss, or signs of lymphadenopathy or Kaposi's sarcoma.

Similar recommendations were made for the plasma centres. For them, the guidelines also recommended:

Donors should be examined for lymphadenopathy. The initial and annual physical should provide an opportunity for an examination by the physician for generalized lymphadenopathy, while a more limited examination should be performed by an adequately trained individual of each donor on the day of plasma collection and a record made of the results of the examination.

An accurate record of each source plasma donor's weight prior to each donation should be made to permit the ready identification of any unexplained weight loss. Any significant unexplained decrease in weight should be considered cause for referral of the donor to a physician for complete evaluation prior to any further plasma collection. Any plasma in storage, which was previously collected from the donor, should be quarantined until the physician's evaluation is complete.

The guidelines recommended that the manufacturers "immediately institute procedures with [their] plasma suppliers to assure that they have adopted appropriate donor screening practices and procedures" as set out in the guidelines to the blood centres and plasma centres.

Although the Food and Drug Administration used the language of requests and recommendations, its guidelines were treated as mandatory. As a result, by the spring of 1983 the U.S. fractionators were not using plasma collected in the high-risk areas identified by Dr Donohue, including prisons. Although there were variations in the measures adopted, all plasma and blood centres, in compliance with the recommendations of 24 March 1983, told the persons from whom they collected plasma and blood about the symptoms of AIDS, described the groups who were at high risk of contracting AIDS, asked the prospective donors whether they had any of the symptoms of AIDS, and told them that anyone who belonged to a high-risk group or had one of the symptoms of AIDS must not give plasma or blood.

Most of the blood centres did not ask donors directly whether they were members of the high-risk groups. An exception was the Irwin Memorial Blood Bank, which in February 1983 began to ask donors whether they had had multiple sexual partners who were intravenous drug users, homosexually active males, or Haitian immigrants, and whether they had resided in Haiti. The New York Blood Center did not ask prospective donors whether they were in the high-risk groups, but in March 1983 it began to tell them which groups were at high risk and offered them a form on which any person who was at high risk could state in confidence that his or her blood should be used only for research. Throughout 1983 and 1984, other blood centres instituted programs in which members of high-risk groups could, after donating, call to say that their blood should not be used in treatment.

After plasma and whole blood were collected, time elapsed before the fresh frozen plasma that was made from them went into the fractionation process, and there was then a period, usually of about six months, between the beginning of the fractionation process and the release by the regulator of the finished blood products. As a result, the measures that were taken by the spring of 1983 to reduce contamination in fresh frozen plasma did not have an effect on the quality of the factor concentrates that were distributed until the autumn of 1983.

On 15–16 December 1983, the blood products advisory committee of the Food and Drug Administration met. Dr Donohue recommended the implementation of a surrogate test for AIDS, using anti-HBc. Representatives of the fractionators had met before his proposal was discussed and had decided to propose a task force to study anti-HBc testing. Cutter's representative, in a memorandum to others at Cutter describing the discussion, stated that "the general thrust of the task force is to provide a delaying tactic for the implementation of further testing." The committee created a task force, and in March 1984 its chair, Dr Rodell, reported in an interim statement that the majority of its members were not in favour of the anti-HBc test. In April 1984, the U.S. Secretary of Health and Human Services announced that HIV had been identified as the causative agent of AIDS and predicted that a specific test for HIV would be widely available within six months. In July 1984, Dr Rodell

submitted the task force's report to the Food and Drug Administration. The majority again opposed implementation of the surrogate test; some members who had previously supported the proposal now opposed surrogate testing because a specific test was expected in the near future.

Few of the plasma and blood centres used anti-HBc as a surrogate test for AIDS. Irwin Memorial Blood Bank and four other blood centres in the San Francisco Bay area introduced it in the spring and early summer of 1984, and in April 1984 Cutter introduced it in the plasma centres it operated. A spokesperson announcing the implementation of the test by Cutter said:

Hepatitis B has been found to be prevalent in the same populations that are at high risk for Acquired Immune Deficiency Syndrome (AIDS) ... and the transmissibility of Hepatitis B seems to parallel that of AIDS. Although not a specific screen for AIDS, since the exact carrier or carriers are not known ... it provides a much more objective basis than has been available in the past to see that plasma from groups at risk for AIDS is not used in the production of coagulation products used by individuals with hemophilia.

Because of the period between the collection of the raw material and the regulatory release of the products, the introduction of anti-HBc testing did not have an effect on the quality of the factor concentrates that were being distributed until the autumn of 1984. Cutter discontinued surrogate testing in January 1985 when testing for the HIV antibody was about to be introduced.

Canadian efforts to reduce the number of plasma units contaminated with AIDS

From 1979 through 1984, the Red Cross collected source plasma through plasmapheresis and separated recovered plasma from the whole blood it collected. During 1983–4, it sent both types of plasma to Cutter and Connaught to be manufactured into factor concentrates. Both the source plasma and the whole blood were donated by volunteers.

Dr Hanna Strawczynski, the chair of the medical and scientific advisory committee of the Canadian Hemophilia Society, attended the 14 January 1983 meeting at which the medical and scientific advisory council of the U.S. National Hemophilia Foundation developed its recommendations to U.S. fractionators and blood centres. On 24 January 1983, she wrote to the members of her committee and said, in part:

The epidemiology of AIDS is strongly suggestive of a blood-borne virus and this is now the working hypothesis of the CDC [Centers for Disease Control]. I have recently attended a meeting of the MASAC [medical and scientific advisory council] of the National Hemophilia Foundation in New York, where recommendations to prevent the disease in patients with hemophilia were discussed and agreed upon ...

The AIDS problem in Canada is of much lesser magnitude, but this may be related to the size of the population and more cases may be expected, including some among our patients.

In view of all this, I have asked the executive of the CHS [Canadian Hemophilia Society] to sponsor a special meeting of the MSAC [medical and scientific advisory committee] to discuss the problems related to AIDS, and a joint meeting with the CRCBTS [Canadian Red Cross blood transfusion service].

The advisory committee met on 7 February. In attendance were members of the committee from all regions of Canada and some lay members of the Canadian Hemophilia Society. Also present were two senior officials of the federal Health Protection Branch: Dr Alastair Clayton, the director general of the Laboratory Centre for Disease Control, which was responsible for monitoring the spread of diseases and recommending actions to control them; and Dr John Furesz, the director of the Bureau of Biologics, which was responsible for regulating blood products, including factor concentrates. The committee drafted recommendations to physicians and to the Red Cross. The draft recommendation to the Red Cross was that

serious effort be made to exclude blood donors who might be at high risk of transmitting AIDS. Suggestions as to how this might be accomplished were:

- a. to expand the CRC BTS [Canadian Red Cross blood transfusion service] voluntary blood donor questionnaire by the inclusion of questions more specifically related to the symptomology of AIDS;
- b. to introduce an educational programme designed toward self exclusion by high risk group blood donors.

After the recommendations had been drafted, the meeting was expanded to include three of the managers from the national office of the Red Cross's blood transfusion service: Dr Martin Davey, the assistant national director; Dr John Derrick; and Dr Derek Naylor, the director of blood products services. They said that the committee's recommendation for modification of the donor-screening questionnaire was acceptable.

During the latter half of February 1983, the draft recommendations were reviewed and amended by members of the advisory committee. The recommendations, in their final form, were issued on 3 March. The recommendations to the Red Cross read as follows:

It is recommended that serious efforts be made to exclude blood donors that might transmit AIDS. These efforts should include:

1. The institution of an educational campaign aimed toward self exclusion of donors belonging to groups at high risk for AIDS as identified to

- date (and any future groups so identified) involving, where possible, the co-operation of the leadership of these groups.
2. An inclusion in the existing blood donor questionnaire of specific questions to detect symptoms associated with AIDS, such as the presence of lymphadenopathy, night sweats or unexplained fevers or weight loss.
3. Evaluation and implementation, when available, of laboratory tests that would identify individuals at high risk of harbouring the AIDS agent.

The committee also recommended that custom-fractionated factor VIII concentrate "be distributed throughout the country in proportion to the number of individuals" who had "never previously received lyophilized [freeze-dried] concentrates" but who needed them for medical or other reasons. The committee wanted to ensure that, in so far as possible, hemophiliacs throughout Canada who had not yet been exposed to AIDS through the use of concentrates would have equitable access to the concentrates that the committee believed were safer because they were made from the plasma of Canadian volunteer donors. The committee also made a series of recommendations to physicians treating hemophiliacs, one of which was as follows:

It is recommended that cryoprecipitate be used to treat those patients with classical [type A] hemophilia who have never previously received lyophilized concentrates. This group includes all newly diagnosed patients regardless of age and severity of hemophilia, and any patient who, for a variety of reasons, has been treated mainly with cryoprecipitate.

Because the Bureau of Biologics did not regulate the collection of whole blood until 1989, it imposed no requirements in 1983 or 1984 on the Red Cross's whole-blood collections to reduce the risk of transmission of AIDS. The bureau did regulate the collection of source plasma, beginning in 1978. In 1983 and 1984 it did not, however, impose any requirement on the Red Cross's source-plasma collections to reduce the risk of transmission of AIDS. It did not require the Red Cross to ask donors whether they were in a high-risk group or whether they had any of the symptoms of AIDS, nor did it require the Red Cross or the fractionators to test blood and plasma donations for anti-HBc. It did not issue guidelines in these matters. Indeed, there is no record that the bureau even considered whether it should issue directives or guidelines that would reduce the risk of infection with AIDS through factor concentrates.

In September 1983, Bioresources Inc., which operated a plasmapheresis centre in Halifax, wrote to the Bureau of Biologics. Much of the source plasma it collected was used to make reagents for clinical tests; some of it, however, was used to make therapeutic hyperimmune globulins. It paid the persons from whom it collected plasma. In its letter, Bioresources described the measures it had taken to reduce the risk that a therapeutic product made from its plasma would cause a user of the product to develop AIDS. It had begun

to distribute written material that described the symptoms of AIDS and listed the high-risk groups, and was asking everyone in the groups or with symptoms to refrain from offering plasma. The persons whose plasma was collected were required to acknowledge in writing that they had read and understood the material. Bioresources had also begun to ask prospective donors whether they had any of the symptoms of AIDS or had been exposed to persons with AIDS. It had also begun to examine each donor for lymphadenopathy every time plasma was collected. Knowledge of the precautions undertaken by Bioresources did not cause the Bureau of Biologics to consider whether the Red Cross should be required to take similar measures in its plasmapheresis program.

The managers of the Canadian Red Cross's blood transfusion service were aware of most of the recommendations that were made and the measures that were taken in the United States to protect the blood supply from contaminated blood and plasma. They had regular contact with the American Red Cross, and received the official reports of, and the recommendations arising from, the important meetings held in that country.

The measures taken by the Red Cross in Canada to reduce the risk of collecting contaminated whole-blood donations, before it was possible to test blood samples for infection with HIV, are reviewed in detail in Chapter 11. The same measures were taken for donations by plasmapheresis; no additional steps were taken to avoid the collection of contaminated source plasma. The rest of this section summarizes the measures that were taken.

On 10 March 1983, the Red Cross issued a press release that asked persons in high-risk groups not to donate blood. The release read, in part:

The Canadian Red Cross Society advises members of groups identified as high risk of carrying Acquired Immunodeficiency Syndrome (AIDS) not to give blood.

These groups are: Patients diagnosed with AIDS, sexual partners of AIDS patients, persons with AIDS symptoms, sexually-active homosexual and bisexual men with multiple partners, recent Haitian immigrants, current or past drug abusers, and sexual partners of individuals at high risk for AIDS ...

The Red Cross is not considering questioning potential donors at blood clinics about their sexual preference or their racial origins.

The Society is, however, asking members of the groups at high risk of developing AIDS to voluntarily exclude themselves from giving blood. All blood donors in Canada are voluntary donors and, as such, represent a group with a highly-developed sense of responsibility to their community. The Red Cross is confident, therefore, that donors finding themselves within the identified risk groups will exercise that sense of responsibility and will refrain from giving blood until such time as the cause and transmission of AIDS can be clarified.

The blood centres in the United States actively excluded persons identified, through their responses to educational pamphlets and questions about symptoms, as being in high-risk groups. The Red Cross responded to the risk of contamination passively through the policy of "voluntary exclusion," which put the burden on members of the high-risk groups not to donate.

In the press release of 10 March 1983, the Red Cross listed "further steps" that it would take to "protect blood recipients from the possible transmission of AIDS through blood." One of them was the "[e]xpansion of the current screening process for blood donors to include specific questions to detect potential donors with symptoms of AIDS or who might be carriers of AIDS." The questionnaire about donors' health was not expanded to include questions about the symptoms of AIDS, despite the statement on 7 February to the medical and scientific advisory committee of the Canadian Hemophilia Society that an expansion of the questionnaire was acceptable and despite the statement in the press release.

Another "further step" that was described in the press release was the "[e]valuation of suitable laboratory tests for AIDS which may become available, with the intention of implementing them as screening measures as soon as possible." This was a reference to surrogate tests. The Red Cross undertook no evaluation of surrogate tests, and anti-HBc testing was not introduced.

A few, but only a few, of the Red Cross medical directors asked organizations in the local gay communities to reinforce the Red Cross's request for voluntary self-exclusion. Dr Derrick wrote a memorandum to some of the medical directors of the seventeen blood centres on 14 July 1983, giving them the names of leaders in their local gay communities who could be asked to support the policy. The memorandum had only a limited effect. Some directors who received the memorandum took little or no action, and others who received it were unsuccessful in making contact. The national office of the blood transfusion service made no attempt to learn what the directors had done or whether they had been successful.

On 1 May 1984, the Red Cross began distributing at its clinics a pamphlet entitled *An Important Message to Our Donors*. The use of the pamphlet was intended as a three-month pilot project. In September 1984, the Red Cross decided to extend the use of the pamphlet for another three months, and in December 1984 it decided to continue to use the pamphlet "on an extended pilot basis" until April 1985. No changes were made to the pamphlet from May 1984 to August 1985. It read, in part:

Recently it has become apparent that the condition known as AIDS (Acquired Immune Deficiency Syndrome) is probably blood borne and should be included in the list of illnesses which excludes donation.

AIDS is a condition in which the body's natural resistance to various diseases is seriously reduced, frequently with fatal results. The cause is unknown. There is no laboratory test to detect it in its early,

non-symptomatic stage. Therefore, it is recommended that for the present, persons who have been indicated, according to current evidence, as being at above average risk of contracting AIDS should not donate blood.

These persons include:

- homosexual or bisexual males who have multiple partners
- present or past abusers of intravenous drugs
- recent immigrants from, or visitors to, those areas where AIDS is endemic, i.e. Chad, Haiti and Zaire
- sexual partners of any of the above persons

If, after reading this pamphlet and the questionnaire, you feel that you should not donate blood at this time you may indicate this to the nurse. *There is no obligation to identify your reason(s) for not donating.* [Emphasis in original.]

The pamphlet did not describe the symptoms of AIDS, which were still not included in the list of questions (the questionnaire mentioned in the pamphlet) that prospective donors were asked about their health. During the summer of 1984, the national office received reports from the blood centres that some donors were not reading the pamphlet thoroughly or at all. Despite these reports, the Red Cross did not require prospective donors to say expressly that they had read the pamphlet before donating. The national office learned in early 1985 that in some centres the pamphlet was not being distributed, and that in others it was being distributed after the blood had been collected.

As in the United States, there was usually a period of six months or more between the collection of the raw materials for blood products and the regulatory release of the finished products. As a result, the press release in March 1983 could not have had any effect on the quality of the custom-fractionated factor concentrates until the autumn of 1983; and the pamphlet, to the extent that it was used after May 1984, could not have had an effect on the quality of the concentrates until late in 1984.

The need to buy commercial concentrates

Not all the plasma collected by the Red Cross was available for fractionation. Some of it was used for transfusion, and some of the plasma that was fresh frozen was used to make cryoprecipitate, which in turn was used for transfusion. Table 14.3 shows the approximate volume of plasma that was available for fractionation from 1978 to 1984. The factor concentrates derived from that plasma were not, however, sufficient to meet all Canadian needs. As a result, the Red Cross had to purchase commercial factor VIII concentrate to meet the total demand. Table 14.4 shows the approximate percentage of the demand that could have been met from Canadian plasma – if it were not for the problems that occurred in the production of custom-fractionated factor VIII concentrate that are described later. As a result of those problems, the actual proportions that were met domestically were somewhat lower than those shown in the table.

Table 14.3
Approximate volume of plasma, in thousands of litres,
available for fractionation from donations collected by
the Canadian Red Cross Society, 1978–84

	1978	1979	1980	1981	1982	1983	1984
Not fresh frozen	97	67	46	44	40	33	34
Fresh frozen, from recovered plasma	31	63	90	88	112	107	111
Fresh frozen, from source plasma	0	0	0	0	2	4	5
Total	128	130	136	132	154	144	150

Source: A report to the Canadian Hematological Society by the Canadian Red Cross Society in 1990

Table 14.4
Approximate proportion of Canadian demand
for factor VIII concentrate that could be met from fresh
frozen plasma collected by the Red Cross, 1979–84 (per cent)

1979	1980	1981	1982	1983	1984
55	55	45	50	45	50

Source: A report to the Canadian Hematological Society by the Canadian Red Cross Society in 1990

The Red Cross began to distribute commercial factor IX concentrate made from U.S. plasma in 1976. In 1979, it began to distribute custom-fractionated factor IX concentrate made from Canadian plasma. By 1981, the Red Cross was distributing only custom-fractionated factor IX concentrate. This was possible because the demand for factor IX concentrate was significantly smaller than that for factor VIII concentrate and could be met from domestic sources of plasma. The Red Cross began to distribute commercial factor VIII concentrate, made from U.S. plasma, and custom-fractionated factor VIII concentrate, made from Canadian plasma, in 1979.

During 1978–84 the amount of fresh frozen plasma available for fractionation increased dramatically as a result of two trends. First, the total amount of fresh frozen plasma produced by the Red Cross increased. Second, the amount of fresh frozen plasma reserved for transfusion or made into cryoprecipitate for transfusion decreased as the treatment of hemophilia moved from plasma and cryoprecipitate to concentrates. Nevertheless, the demand

for concentrates increased more rapidly than the supply of available fresh frozen Canadian plasma, and Canada's dependence upon imported factor VIII concentrate persisted.

The use of plasmapheresis to decrease the dependence on commercial concentrates

In September 1976, the Minister of National Health and Welfare proposed self-sufficiency as one of the governing principles for the blood supply system. During the autumn of 1976, the Red Cross and representatives of all the provinces endorsed that principle.

Domestic demand could not be met, however, from the plasma recovered from whole-blood donations. In order to move towards self-sufficiency, it was necessary to collect source plasma by plasmapheresis, and in 1979, after a successful pilot project, the Red Cross began a plasmapheresis program for this purpose. It did not allocate any of the fresh frozen plasma made from source plasma for fractionation until 1982, but even before that date the new program was having an effect. The fresh frozen plasma derived from plasmapheresis was used for transfusion, freeing fresh frozen plasma recovered from whole blood for fractionation.

By 1982, the Red Cross was making 7,831 plasmapheresis collections per year. It had bought equipment, hired and trained staff, and recruited plasmapheresis donors. More was required and expected of those donors than of donors who gave whole blood; a unit of plasma took much longer to collect than a unit of whole blood, and donations could be made much more frequently – approximately twenty-five times per year, compared with a maximum of four times per year for whole blood. Further expansion of the program required greater efforts in recruitment, but the pool of dedicated plasmapheresis donors could not be increased overnight.

The expansion of the plasmapheresis program also required an investment of money, which would have to be approved by the Canadian Blood Committee, through which the provinces funded the national blood program. In its annual budget proposal for 1983, the Red Cross asked for the resources that would enable it to make 24,000 plasmapheresis collections that year. On 3 March 1983, the medical and scientific advisory committee of the Canadian Hemophilia Society, in a recommendation addressed to the Canadian Blood Committee, supported an increase in the supply of domestic plasma:

Epidemiologic evidence from the USA suggests that certain groups in that country are at risk both to contract AIDS and to transmit it if they act as blood donors. The incidence of AIDS in the USA is threefold higher than in Canada at this time. In view of this information, it is recommended that urgent steps be taken to expedite the attainment of self-sufficiency in the production of Canadian voluntary donor plasma and plasma fractionation products.

At a meeting on 22–23 March 1983, the Canadian Blood Committee approved the Red Cross budget with one major modification. It approved only enough funding to permit 12,000 plasmapheresis collections, one-half the number requested. An analysis of the Red Cross budget, prepared at the committee's request, said that the advantages of increasing the number of plasmapheresis collections to pursue self-sufficiency in factor VIII concentrate "have to be weighed against the high cost of plasma procurement plus the costs of plasma processing and the cost of sustaining or increasing already high inventory levels of other products." The concern expressed about the levels of other products was a reference to the fact that, if more source plasma was collected through plasmapheresis and then fractionated, more albumin than was required would be produced. (Albumin is a blood product, used as a volume expander in cases of traumatic blood loss and in treating severe burns.) The minutes recording the committee's decision note that limiting the collections to 12,000

will delay progress towards self-sufficiency, particularly for factor VIII. A supplementary purchase of approximately 22 million AHF [antihemophilic factor] units is required again for 1983. The pheresis system will not operate at optimal efficiency; however, the reduced activity will not add to the growing inventory in albumin. Security of supply will not be jeopardized.

In its annual budget proposal for 1984, the Red Cross again asked for the resources to increase plasmapheresis collections, this time to 24,280. The Canadian Blood Committee approved funding for 12,140. Its decision, according to its minutes, was based on "savings of approximately \$400,000 for supplies, \$25,000 for laboratory costs and \$100,000 for equipment." The committee reconsidered its decision in August 1984 and agreed to funding that would permit an increase in the number of collections for the year to 16,140.

In both 1983 and 1984, the Red Cross did not collect as many units of source plasma as the Canadian Blood Committee had approved. It collected 10,651 units in 1983 and 14,553 units in 1984. The number of collections allowed in the budgets for those years was not achieved because, after each approval, it took time to increase the pool of dedicated plasmapheresis donors.

The brands of concentrate distributed

Four fractionators made non-heat-treated concentrates for the Red Cross between 1978 and 1985. Three were U.S. fractionators, Hyland, Cutter, and Armour; the fourth was the one active Canadian fractionator, Connaught. The suppliers and their products appear in Table 14.5. Custom-fractionated concentrates were made entirely from plasma collected from volunteer Canadian donors through the Red Cross; commercial concentrates were derived from plasma from other sources involving both paid and unpaid U.S. donors.

Table 14.5

Suppliers of factor concentrates to the Canadian Red Cross Society, 1978–85

	Factor VIII commercial	Factor VIII custom fractionated	Factor IX commercial	Factor IX custom fractionated
Hyland	1979–84	1979	1978–79	1979
Cutter	1979–85	1980–85	1978–81	1980–85
Armour	1984–85			
Connaught	1983–85	1980–85		1979–85

Source: Canadian Red Cross Society inventory records

The Red Cross did not distribute the products of all its suppliers throughout Canada. All Connaught's factor VIII concentrates were distributed in Ontario. In the late 1970s, the government of Ontario had supported Connaught when Connaught and the Red Cross were rivals, each attempting to become Canada's sole domestic fractionator, a history reviewed in Chapter 4. The Ontario government took the position that, at a minimum, all plasma collected in Ontario should be fractionated by Connaught. When the Red Cross and Connaught negotiated their custom-fractionation contracts, it was understood that the fresh frozen plasma collected in Ontario would be fractionated by Connaught and that Connaught's custom-fractionated factor VIII concentrate would be distributed only in Ontario. The understanding did not apply to Connaught's custom-fractionated factor IX concentrate, made from fresh frozen plasma collected throughout Canada; it was distributed throughout the country. For reasons that are not apparent, Connaught's commercial factor VIII concentrate also was distributed only in Ontario, even though it was not made from Canadian plasma and so was not subject to the understanding. Because Connaught's capacity could not fully meet the needs of Ontario, residents of that province also received both custom-fractionated and commercial factor VIII concentrates made by the U.S. manufacturers.

With one exception, the other provinces received both custom-fractionated and commercial factor VIII concentrates manufactured by the U.S. corporations. The exception was Nova Scotia, which, for reasons that cannot be determined, received only custom-fractionated products.

Difficulties in production at Connaught

The Red Cross and Connaught entered into a custom-fractionation contract for 1981–3 under which the Red Cross agreed to deliver 70,000 litres of plasma (at least 35,000 litres of which was to be fresh frozen) per year, and Connaught

agreed to produce, as finished concentrate, a minimum of 160 units of factor VIII for every litre of fresh frozen plasma it received. The plasma that was not fresh frozen was used to manufacture other blood products. If the minimum yield of factor VIII concentrate was not achieved, Connaught would supply the Red Cross "free of charge quantities of product meeting the specifications provided for in this agreement." Connaught could compensate the Red Cross for any shortage in production in two ways. It could produce additional factor VIII concentrate from plasma obtained from a source other than the Red Cross, or it could make a cash payment that would enable the Red Cross to obtain factor VIII concentrate from another manufacturer.

Connaught did not achieve the minimum yield of factor VIII concentrate specified in the contract. The shortage, by the end of the contract, was 6.6 million units, approximately 40 per cent of the specified minimum. Connaught compensated the Red Cross in both of the possible ways. By September 1984, it delivered approximately 2.3 million units of commercial factor VIII concentrate, which it had made from U.S. plasma. It also paid approximately \$450,000 to the Red Cross, with which the Red Cross bought approximately 4.3 million units of factor VIII concentrate made by U.S. fractionators from U.S. plasma.

When it entered into the contract, Connaught knew that the small scale of its operations would limit its yield. Connaught's product lots were smaller than those of the U.S. manufacturers who supplied concentrates to the Red Cross. As a result, Connaught had to reserve a higher proportion of the finished product from each lot for testing by its own quality control staff and by the Bureau of Biologics. Connaught also lost a higher percentage of raw material as "dead volume," plasma unavoidably left behind in the processing equipment. Furthermore, some of Connaught's lots of factor VIII concentrate were not readily soluble. This proved to be an increasingly serious problem that resulted in the destruction of substandard lots of factor VIII concentrate and a significant reduction in total yield.

By the end of 1982, the Red Cross was receiving complaints about the quality of Connaught's factor VIII concentrate. Users complained about the lack of solubility; about the adverse reactions of blurred vision, headaches, dizziness, fainting, fever, and rashes; and about rubber stoppers that "cored" into the concentrate when the needle of the administration set was inserted through them.

At the beginning of 1983, the Red Cross purchased 18 million units of commercial factor VIII concentrate to supplement the custom-fractionated products made from Canadian donations. It ordered 6 million units, one-third of the total, from Connaught. There were two reasons why it did so, despite the complaints it had received about Connaught's custom-fractionated products and Connaught's problems in production. The Red Cross hoped that the increased volume would help Connaught solve its problems in production.

It also wanted to improve its relationship with Connaught, to which it was bound by a decision of the ministers of health that Connaught should receive 50 per cent of all Canadian-collected plasma for custom fractionation.

When its first contract with Connaught for custom-fractionated concentrate came to an end in 1983, the Red Cross entered into a second, for 1984–5, but only because the ministers of health had required it to use Connaught as a custom fractionator. Connaught had not solved its production problems, and the Red Cross would have preferred to have all its custom fractionation done by one or more of the U.S. manufacturers.

In the new contract, the Red Cross agreed to deliver 75,000 litres of plasma (at least 45,000 litres of which was to be fresh frozen) in 1984 and 80,000 litres of plasma (at least 55,000 litres of which was to be fresh frozen) in 1985, and Connaught again agreed to produce, as finished concentrate, a minimum of 160 units of factor VIII per litre of fresh frozen plasma. As in the earlier contract, if the minimum yield was not achieved, Connaught had to compensate the Red Cross for the shortage. During the term of this contract, the problem of lack of solubility occurred in an increasing number of production lots, with the result that large amounts of concentrate had to be discarded. By the end of 1984, Connaught was already approximately 4.4 million units (65 per cent) short of the agreed minimum yield. On 16 November 1984, the Bureau of Biologics required the Red Cross to convert its national distribution to heat-treated factor concentrates. In that month, the Red Cross stopped shipping fresh frozen plasma to Connaught, which had not yet developed a process to manufacture heat-treated concentrates. Connaught delivered the last lot of non-heat-treated factor VIII concentrate to the Red Cross on 12 April 1985.

Because Connaught's custom-fractionated factor VIII concentrate was distributed in Ontario only, its difficulties in production did not affect other provinces. In Ontario, however, the dependence on factor VIII concentrate made from U.S. plasma rose from a target of approximately 50 per cent (which would have been reached had Connaught been able to achieve the minimum yield of custom-fractionated concentrate envisaged in the contract) to somewhat more than 80 per cent.

Concerns about plasma from U.S. prisons

In 1978, Connaught had made plans to obtain plasma from U.S. plasma centres. It intended to buy the plasma directly from the centres, with its own staff members inspecting each centre before it was approved as a supplier. Beginning in 1980, it inspected the U.S. centres from which it was to receive plasma.

In the autumn of 1982, Connaught entered into two contracts that changed the way in which it approved U.S. centres. In the first contract, Connaught agreed to buy 27,780 litres of U.S. fresh frozen plasma from Cryosan Inc. of Massachusetts and to sell 50,000 vials of albumin made from that plasma to

Cryosan Inc. for distribution in the United States. All the plasma was to come from centres licensed by the Food and Drug Administration. The fresh frozen plasma bought by Connaught under this agreement was supplied through the Continental Pharma Division of Cryosan Ltd. (later Continental Pharma Cryosan Inc.), a Montreal plasma broker that was related to Cryosan Inc.

Cryosan Ltd. and its related corporations were major plasma traders. Cryosan Ltd. was the largest Canadian importer of plasma throughout the period 1981–5, during which it imported plasma worth approximately \$22 million from Belgium, France, Germany, Italy, Spain, and the United States. Of the plasma it imported, all but a small amount of the U.S. plasma was exported. Cryosan Ltd. was also a major shareholder in a large U.S. plasma collector, North American Biological Inc. In a filing with U.S. securities officials, the management of North American Biological Inc. described the corporation as “the largest independent [non-fractionator] supplier of source plasma in the world.” During the period 1981–5 it collected approximately 300,000 litres per year – between 5 and 10 per cent of all source plasma collected in the United States – in its U.S. centres. In 1984, Continental Pharma Cryosan Inc. acquired a controlling interest in North American Biological Inc.

The second contract Connaught entered into was with the Red Cross, as described above, to supply 6 million units of commercial factor VIII concentrate during 1983. The contract required that the U.S. plasma used to make the concentrate come from centres licensed by the Food and Drug Administration. To produce 6 million units of factor VIII concentrate, Connaught required large amounts of fresh frozen plasma; at a yield of 160 units per litre of plasma, more than 37,500 litres would be needed. The volume of plasma needed changed the way in which Connaught approved U.S. plasma centres. Some of the plasma was supplied through Cryosan Ltd. In its written submission, Connaught described the consequences of suddenly needing to acquire large amounts of fresh frozen plasma:

The short-term requirements for plasma necessitated approval of some centres which, due to their inability to meet Connaught's criteria for volume or price, could only supply Connaught with product on one occasion. It was impracticable for Connaught to send a member of its Quality Assurance ... department to inspect each of these centres for a one time “spot” purchase.

Instead of sending its own employees to inspect the centres before accepting plasma from them, Connaught planned a new procedure. It would confirm that each centre that was a potential plasma supplier had a valid licence from the Food and Drug Administration; it would obtain and review the Food and Drug Administration's inspection reports for the centre; it would approve a centre if the reports showed that it was satisfactory, or, if the reports left important questions unanswered, approval would come only

after an inspection by Connaught employees; and it would reject a centre if the inspection reports revealed that it was unsatisfactory. Connaught did not follow the planned procedure. To use the words of a Connaught official who testified at the hearings, "Obviously the system broke down." The Food and Drug Administration inspection reports were obtained, but they were not reviewed.

The Bureau of Biologics did not require Connaught to inspect the U.S. centres from which it obtained plasma, even if the finished blood products made from the plasma were to be distributed in Canada, but simply required that each centre be licensed by the U.S. Food and Drug Administration. At least once each year, Connaught gave the bureau a list of all the centres from which it might obtain plasma. Connaught also gave the bureau a list of all the centres from which plasma had been obtained for each of its lots of finished blood products, including factor concentrates.

One of the centres used by Connaught was in Grady, Arkansas, where the state Department of Corrections had a prison. A plasma centre, licensed by the Food and Drug Administration, had for several years been operating within the prison, collecting plasma from inmates. In the early 1980s, the Department of Corrections employed Health Management Associates Inc. of Pine Bluff, Arkansas, to manage its centre.

In mid-June 1983, Health Management Associates told the Food and Drug Administration that thirty-eight units of plasma, taken from four inmates of the Grady prison, should not have been collected. Blood samples from the four inmates had been tested at the time of collection for the surface antigen of hepatitis B, an indicator of current infection with hepatitis B. The four inmates had tested negative for the surface antigen when their plasma was collected. However, during a review of old records it had been found that they had previously tested positive. All thirty-eight units had been sent to Continental Pharma. Health Management Associates took the position with the Food and Drug Administration that, because the four inmates had tested negative for the surface antigen when the units in question were collected, "the health hazard is very remote," and there should therefore be no need to recall the units. Hepatitis B is a serious disease, and the discovery that plasma had been received from four inmates who had previously tested positive for it was important, but the more recent negative tests suggested that it was unlikely that the inmate donors were still infectious with hepatitis B and that their plasma would transmit that disease. By 1983, however, an association had been identified between hepatitis B and AIDS; most persons with AIDS had also been infected with hepatitis B. There was a greater than average risk that the thirty-eight units of plasma from the four inmates could transmit AIDS.

On 17 June 1983, within days of learning of the problem, Health Management Associates told Continental Pharma about the previous test results. Four of the thirty-eight units had been shipped to Connaught, one on 26 February

and the other three on 17 March 1983. (The other thirty-four units had been sold to corporations in Switzerland, Spain, Japan, and Italy.) Continental Pharma did not, in turn, tell Connaught about the problem because it believed that the risk of transmission of hepatitis B from the plasma in question was no greater than the risk from any unit that tested negative for the surface antigen at the time of collection.

Two lots of Connaught's commercial factor VIII concentrate had been made from plasma pools that contained the four units. Those lots had been delivered to the Red Cross on 24 May and 28 June.

Health Management Associates eventually decided that it should voluntarily withdraw the thirty-eight units of plasma, and on 11 August 1983 the Food and Drug Administration concurred. On 16 August, the Food and Drug Administration told the Health Protection Branch of the Department of National Health and Welfare in Ottawa that Health Management Associates was voluntarily withdrawing the thirty-eight units of plasma, that Continental Pharma was the sole consignee of them, and that four of the units had gone to Connaught. On 18 August, the Health Protection Branch told Connaught about the problem. This was the first time that Connaught was aware of it.

The next day, 19 August 1983, the director of scientific, medical, and regulatory affairs at Continental Pharma told Connaught of the problem. According to the Connaught memorandum of the conversation, he said:

Four donors who were RIA [radio-immune assay] negative for approximately one year were found on subsequent investigation to have been RIA positive some four to five years earlier and were really not eligible to be donors of plasma at all. Most of the donors in these groups were from a prison population and had not been truthful when their history was taken.

Until this conversation, Connaught had not been aware of the fact that it had been processing plasma collected from prison inmates. The shipping papers accompanying the plasma had not revealed that the centre was located in a prison. They had simply referred to the source as the "ADC Plasma Center, Grady, Arkansas," without any indication that "ADC" stood for "Arkansas Department of Corrections." An inspection report of the Food and Drug Administration that Connaught had received in February 1983 revealed that the centre was in a prison, but it had not been reviewed.

On 23 August 1983, Connaught told the Red Cross that four units of plasma had been collected from persons who had tested negative for hepatitis B at the time of the collection but who had tested positive previously. Connaught said that, in view of the earlier test results, "we consider it prudent to voluntarily withdraw this material."

Of the 2,409 vials in the two lots that contained the four plasma units, only 417 were retrieved in the withdrawal. If Connaught had been made aware of the problem in mid-June, when Health Management Associates reported

it to the Food and Drug Administration and Continental Pharma, at least 983 additional vials could have been retrieved because they would not yet have left the Connaught warehouse.

In late August 1983, Health Management Associates told the Food and Drug Administration that it had discovered that plasma had been collected from a fifth inmate of the Grady prison who had previously tested positive for hepatitis B. Thirty-four units had been collected from him between July 1982 and May 1983; all had been consigned to Continental Pharma. On 31 August, the Food and Drug Administration told the Health Protection Branch about this new information. On 1 September 1983, Continental Pharma told Connaught, and gave it the identification numbers of six units that had been delivered to Connaught – three on 23 November 1982, one on 26 February 1983, and two on 17 March 1983. By 6 September 1983, Connaught had identified two lots of factor VIII concentrate that had been made from plasma pools containing the six units. They had been delivered to the Red Cross on 12 February and 2 March 1983. On 6 September, Connaught asked the Red Cross to withdraw these lots, which had contained 1,968 vials. Only twenty-seven of those vials were retrieved.

On 7 September 1983, a vice-president of Connaught told the Red Cross that the plasma that had led to the withdrawals had been collected from prison inmates. Dr Davey, the assistant national director of the blood transfusion service, on behalf of the Red Cross, cancelled the contract for commercial concentrate with Connaught on the same day. In a letter to Connaught, he wrote:

The immediate cause of this action is your recall, within the past two weeks, of four lots of concentrate delivered earlier this year, because of the possible contamination of the plasma pools with hepatitis B. While the CRC [Canadian Red Cross] agreed with your action, and will cooperate fully in the recall and reconciliation of these lots, it leaves us with no confidence in the quality and safety of the material. In addition, as much of this material has already been distributed and used, physicians and patients who learn of the recalls are alarmed about possible consequences, and will be unwilling to continue to use concentrate from the same source. The recalls have also prejudiced the continuity of supply of AHF [anti-hemophilic factor] throughout Ontario ...

It is acknowledged that Connaught is not directly responsible for the circumstances that led to these product recalls, and has acted in good faith and with expedition to effect them. They have, however, so eroded CRC and user confidence in this product that we cannot continue to accept it, and will be making early arrangements with another supplier.

Although it was not expressly stated by Dr Davey in his letter, it is clear from his testimony and from other documentary evidence that one of the reasons for the cancellation of the contract was that Connaught had used plasma that had been collected from prison inmates.

During September, Connaught's director of quality control and regulatory affairs reviewed the approvals that had been given for the receipt of plasma from U.S. centres. He found that Connaught's approval process had broken down. Plasma that had been used to make products had been accepted from twelve centres that had never been properly approved in accordance with Connaught's procedures. One of them was the prison centre located at Grady, Arkansas. In a memorandum to the employee responsible for Connaught's approval of centres, the director of quality control and regulatory affairs wrote:

I have studied the Inspection Report on the Centre at the Arkansas Department of Correction which you received through FOI [Freedom of Information]. I find the report raises sufficient serious questions that you or whoever in your group reviewed it should have done some additional investigation before approving the Centre.

The receipt of an FOI report which just does not indicate revocation of the Centre's licence should not be taken as sufficient evidence that that Centre is acceptable to our standards.

You have yourself, together with me and alone, turned down centres which have passed by the U.S. inspection. I consider the blanket approval of this Centre, whether done by you or a member of your staff, as entirely unacceptable.

The review revealed that some of the plasma processed by Connaught had been collected from inmates of four other prisons, in Louisiana. The plasma centres in those prisons were operated by Community Plasma Center Inc., which had sold the plasma it collected to Health Management Associates, which in turn had sold the units in question to Continental Pharma, which had sold them to Connaught, where they had been received from November 1982 to January 1983. Moreover, in August 1983, Connaught had bought 9,000 litres of plasma directly from Community Plasma Center. By September 1983, Connaught had four pools of plasma in process that contained units collected from inmates in Louisiana, had in its warehouse 6,000 litres of plasma purchased from Community Plasma Center that had not yet been pooled, and was awaiting delivery of an additional 3,000 litres that were in transit. Connaught made sure that no factor concentrate was made from the pools that contained the plasma from Louisiana prisons, and it returned the 9,000 litres that had not been pooled. Connaught had received reports of the Food and Drug Administration for the centres in the four Louisiana prisons in February 1983. The reports revealed that all four centres were located in prisons, but, again, the reports had not been reviewed.

The review by the directors of quality control and regulatory affairs in September 1983 also revealed that Connaught was about to receive plasma from many centres that it had never approved. A shipment from Plasma Services of Scottsdale, Arizona, was expected in September that was to contain plasma collected in as many as 100 centres. None of the centres had been approved by Connaught. When this shipment arrived, it was isolated until the centres were properly approved in accordance with Connaught's procedures.

Concerns about plasma from San Francisco

Soon after it entered into the contract for commercial concentrate, Connaught sought to assure the Red Cross that the U.S. plasma it used would not be collected in areas where there was a high prevalence of AIDS. On 23 March 1983, the head of its fractionation program wrote to Dr Naylor, the director of blood products services, that "none of these suppliers [of plasma] are located in population centres in the United States shown to be at high risk for AIDS ... We are keenly aware of the potential risk of AIDS for the hemophiliac."

San Francisco had been identified as a high-risk area for AIDS by that time. Connaught began to receive plasma from the Irwin Memorial Blood Bank (Irwin Memorial) some time between the beginning of February and the end of May 1983. Connaught's statement of 23 March was either inaccurate at the time it was given or became inaccurate soon afterwards. The Red Cross was not told until February 1984 that Connaught was receiving plasma from Irwin Memorial.

The plasma from Irwin Memorial was supplied through a broker. In June 1983, a person working in the fractionation program at Connaught noted that some of the plasma supplied by the broker had been collected by Irwin Memorial and said in a memorandum to the head of Connaught's fractionation program that "some action may be required to assure ourselves that the plasma is clean." The head of the fractionation program replied that a member of the quality assurance department would speak to the broker "about removing this source." Irwin Memorial was not removed as a supplier of plasma; a member of the quality assurance team communicated with Irwin Memorial directly, and, after receiving assurances that it was producing safe plasma, Connaught retained it as a supplier.

When Connaught reviewed the approval of its plasma suppliers in September 1983, it used two criteria in choosing suppliers: that there was a satisfactory inspection report from the Food and Drug Administration on file or that a satisfactory inspection by Connaught employees had been conducted and "we are satisfied that the supplier is making every reasonable effort to ensure that donors do not suffer from AIDS disease." That the suppliers were not collecting plasma in an area of high risk for AIDS was not a consideration.

Irwin Memorial was approved as a plasma supplier in the review. At that time, fourteen of the forty plasma pools in process at Connaught contained plasma collected at Irwin Memorial. The fourteen lots contained no plasma

from a supplier that had been rejected in the review, and the processing of factor VIII concentrate from those lots therefore continued.

On 17 November 1983, Connaught gave a list of its approved suppliers, including Irwin Memorial, to the Bureau of Biologics. Connaught also listed Irwin Memorial as one of its suppliers in three filings with the bureau in 1984 and one in 1985. The bureau did not review the lists.

The difficulties Connaught faced in meeting its contractual obligations with the Red Cross to supply custom-fractionated factor VIII concentrate have already been described. By 14 December 1983, it was apparent that Connaught would be at least 4.5 million units short of its obligations under that contract, and on that day it asked if it could make up some of the shortfall by delivering commercial factor VIII concentrate made from U.S. plasma. The Red Cross agreed, despite the problems that had led to the cancellation of Connaught's contract for commercial concentrate three months earlier, but only if it approved the suppliers of the plasma to be used.

On 21 February 1984, Connaught's director of quality control and regulatory affairs wrote to Dr Naylor with a list of the suppliers. It included Irwin Memorial. A revised list, which again included Irwin Memorial, was sent to the Red Cross on 2 April 1984. The Red Cross did not tell Connaught that Irwin Memorial was unacceptable as a plasma supplier.

By the end of 1984, approximately 700 persons in San Francisco had developed AIDS. In collaboration with the city's department of public health, Irwin Memorial conducted a study, during which it reviewed its records and found that twenty-seven of those persons had donated blood during the period 1979–84, many of them more than once. In a letter to Connaught dated 21 November 1984, the scientific director of Irwin Memorial wrote:

The purpose of our study ... is to determine the risk to the recipient of blood components from such donors, the co-factors which determine susceptibility, and the tests which may be useful in prognosis and management. In our retrospective search of files on these donors, we inevitably discovered that many had donated plasma which had been sent for fractionation. I discussed the need to report such cases with Dr Donohue of the FDA [Food and Drug Administration]. His answer was that we were obligated to report them to the manufacturer with a copy to the FDA.

Among the plasma shipments were three batches sent to Connaught. The details on those batches are on the attached print-out. The donors met all the criteria in effect at the time they donated, and the donation[s] occurred as recently as May, 1983. They denied reasons to exclude themselves after procedures exceeding those recommended by the FDA and AABB [American Association of Blood Banks] had been followed.

The letter was received by Connaught three weeks later, on 11 December, but the attachment did not include the identification numbers of the units that Connaught needed to trace them. Three weeks later, on 4 January 1985,

Connaught received the identification numbers. By 8 January, Connaught had determined that the three plasma units had gone into two pools, which had been used to make four lots of factor VIII concentrate. One lot had been destroyed because of production problems. The other three lots had been delivered to the Red Cross.

On 10 January 1985, the Red Cross was told of the problem and began analysing the distribution of the three lots. By 15 January, the following facts had been determined: the first lot, of 965 vials, was received by the Red Cross on 16 August 1983, was distributed to blood centres in Ontario during August, and was recalled, with 208 vials retrieved, for reasons unrelated to Irwin Memorial; the second lot, of 1,172 vials, was received on 28 November 1983 and was distributed to blood centres in Ontario in mid-February 1984; the third lot, of 1,189 vials, was received on 27 April 1984 and was distributed to blood centres in Ontario during May and June.

On 11 January 1985, Connaught's director of clinical and medical affairs wrote a memorandum recording the content of conversations he had had that day with officials of the Red Cross and the Bureau of Biologics. The conclusion of the memorandum is set out below. Lot 36249, which had an expiry date of January 1985, was the lot that was received by the Red Cross on 27 April 1984.

In my communication with Dr Boucher [head of the blood products division of the Bureau of Biologics], he thanked me for having informed him but did not feel very strongly that there was any great problem with these findings as the AIDS virus (HTLV-III) [HIV] was very labile and would probably succumb to the processing of the product. He was to leave a file note for Dr Furesz [the director of the Bureau of Biologics] and was expecting a note from [Connaught's director of quality control and regulatory affairs] on this matter.

Dr M. Davey, Canadian Red Cross, received the information calmly and recognized that these findings were probably not infrequent and there was really not much that could be done about it. He was to put a tracer on lot 36249 as that lot was still in circulation, though he doubted whether any of these lots were still available – some of the latter lot could be in some hemophiliac's refrigerator at home.

Dr Wark Boucher's note of the telephone conversation with Connaught's director of clinical and medical affairs reads, in part:

I agreed with [Connaught's director of clinical and medical affairs] that no further action seemed necessary at this time. [Connaught's director of clinical and medical affairs] was going to call Dr M. Davey, Canadian Red Cross, and inform him.

On 15 January 1985, the Red Cross gave its analysis of the distribution of the three lots to the Bureau of Biologics and to Connaught. According to Dr Boucher's notes, he was told by Dr Davey during a telephone conversation that day that

in his [Dr Davey's] opinion lot 36249-1 will have been used, all ampoules would be in the hands of users and any attempt to recover what would amount to only a few vials would raise undue concerns among the population. If any vials had been in the centres, they would have removed these vials.

On the same day, Dr Davey wrote to Connaught and said:

As it is believed that all the material distributed has already been used, no further action will be taken unless the HPB [Health Protection Branch] requires a formal recall. Dr W. Boucher of the Canadian Bureau of Biologics today informed me that the Bureau of Biologics will not request this.

On 22 February 1985, Connaught's director of quality control and regulatory affairs wrote letters to the Red Cross and the Bureau of Biologics, reviewing what Connaught had learned about the three lots. The letter to the Red Cross included the fact that "[n]o further action has been taken on these lots." He concluded the letter to the bureau by saying: "We were informed by Dr Davey of the Canadian Red Cross that no further action is required on these lots. A copy of a letter to this effect from Dr Davey, dated January 15, 1985, is attached."

Connaught's responses to measures taken in the United States to reduce risk

On 12 January 1983, an employee of Connaught asked the Food and Drug Administration what directives it had issued in this connection, and was told that there had been none. Connaught therefore remained unaware that the U.S. fractionators had voluntarily complied with the Food and Drug Administration's request not to use source plasma collected in prisons or recovered plasma from Irwin Memorial. According to the Connaught memorandum describing the telephone conversation, the employee was told, "Don't panic – yet."

On 29 March 1983, Connaught's quality control department received a copy of the guidelines that the Food and Drug Administration had issued five days earlier. On 13 April 1983, Connaught wrote to some of its plasma suppliers, asking for confirmation that prospective donors were all "given information about AIDS and that they have the opportunity to exclude themselves from the routine plasma programme." From the list of those to whom the letter was sent and from the review conducted in September 1983, it is

clear that the letter was not sent to all Connaught's plasma suppliers. More particularly, it was not sent to the five prison centres from which Connaught received plasma. In September 1983, Connaught asked for written confirmation, from those centres that were retained as suppliers after the review, that they were complying with the guidelines that had been issued by the Food and Drug Administration in March 1983.

During the same month, as part of the review, Connaught's director of quality control and regulatory affairs visited the Office of Biologics, the counterpart in the U.S. Food and Drug Administration of the Canadian Bureau of Biologics. He learned that, although it was not illegal in the United States to distribute products made from plasma collected from prison inmates, it was considered most imprudent to do so, even though the Food and Drug Administration was still renewing licences for centres located in prisons. One of the reasons why it was considered imprudent, according to his memorandum of the discussions, was that the use of such plasma to make factor concentrates presented "a definitive risk" of causing AIDS because of the high rate of AIDS among prison inmates. He also learned that the U.S. fractionators had stopped using plasma collected from prison inmates early in 1983. The director concluded his memorandum by saying:

Connaught Laboratories Limited have at no time violated FDA [Food and Drug Administration] regulations in this case. We were unaware of the fact that the plasma came from penitentiary centres and were not informed of the U.S. manufacturers' ... decision with respect to such plasma.

Our decision [now] to follow the American fractionators' example was considered not only prudent but essential.

Disclosure of the risk of AIDS

When fractionators prepared their vials of factor concentrate in packages for shipping, they included printed information about the concentrates, their proper use, and possible risks in using them. In the autumn of 1983 and in early 1984, U.S. fractionators added warnings about the risk of AIDS to the information in the product inserts – Armour, for its factor VIII concentrate, in October 1983; Cutter, for its commercial factor VIII concentrate, in January 1984; and Hyland, for its factor VIII concentrate, in March 1984.

The Red Cross received commercial factor VIII concentrate that was made by Armour during most of 1984, and most, if not all, of it had a warning about AIDS in the product inserts. It received commercial factor VIII concentrate made by Cutter throughout 1983, 1984, and the first four months of 1985 and, beginning with the shipments that were received in the spring of 1984, the product inserts contained a warning about the risk of AIDS. It received commercial factor VIII concentrate made by Hyland throughout 1983 and in January 1984, but all these shipments were made before Hyland added a warning about AIDS to its product inserts.

Cutter told the Red Cross on 14 December 1983 that it was adding a warning about the risk from AIDS to the product inserts for its commercial concentrates, and asked whether a similar warning should appear in the inserts for the custom-fractionated concentrates Cutter was making for the Red Cross. On 10 January 1984, representatives of the Red Cross and Cutter met to discuss this question, among others. The Red Cross's memorandum of the meeting included the following comment:

The CRCBTS [Canadian Red Cross blood transfusion service] does not wish Cutter to include a statement referring to the possible transmission of AIDS on product inserts for CRC sourced Factor VIII and Factor IX. Such a statement may be appropriate for Canadian products and will be considered when standard packaging formats are drawn up.

On 19 April 1984, the national office of the Red Cross blood transfusion service distributed a memorandum to the medical directors of its seventeen blood centres that told them that Cutter's commercial factor VIII concentrate now included a warning about AIDS, set out the text of the warning, and then stated:

Please be advised that the inclusion of this statement was a corporate decision by Cutter intended to limit their product liability and in no way indicates any change in their method of obtaining plasma or processing it.

The product inserts for the non-heat-treated custom-fractionated factor VIII and factor IX concentrates made by Cutter and distributed by the Red Cross during the period 1983–5 did not include warnings about AIDS. Nor did the product inserts for the non-heat-treated commercial factor VIII, custom-fractionated factor VIII, and custom-fractionated factor IX concentrates made by Connaught and distributed by the Red Cross during the period 1983–5.

An analysis of events in the United States

In July 1995, the U.S. Institute of Medicine published a report on the contamination of the U.S. blood supply in the 1980s entitled *HIV and the Blood Supply: An Analysis of Decisionmaking*. Its findings are significant to Canada because approximately half the factor concentrates on which Canadian hemophiliacs depended came from the United States. The committee that made the report reviewed the measures taken to avoid the collection of plasma and blood from persons who were members of high-risk groups and reached the following conclusions:

When confronted with a range of options for using donor screening and deferral to reduce the probability of spreading HIV through the blood supply, blood bank officials and federal authorities consistently chose the least aggressive option that was justifiable.

In adopting this limited approach, responsible officials rejected options that may have slowed the spread of HIV to individuals with hemophilia and other recipients of blood and blood products. Among these options were asking male donors about sexual activity with other men and screening donated blood for the anti-HBc antibody. The Committee believes that both of these activities were reasonable to require in January 1983.

... lack of consensus about the method of HIV transmission, the natural history of HIV-related disease, and the consequences of alternative modes of intervention to prevent its transmission was an important factor in decisionmaking on donor screening and deferral. There was, for example, uncertainty about the sensitivity and specificity of anti-HBc screening as a method for identifying high-risk donors ...

The absence of consensus on ... basic matters of epidemiology led to second-order disagreements about the costs and benefits of alternative actions. These cost-benefit calculations were often hidden and unspoken. Indeed, the Committee suspects that many of those arguing alternative views would have been surprised and uncomfortable if told they were actually engaged in a dispute over cost-benefit calculations. However, as they projected the scenarios about what would happen if they undertook one strategy or another (e.g., the implementation of a [surrogate] test, the deferral of a high-risk group) and drew conclusions about the desirability of those scenarios, they were, in effect, tallying advantages and disadvantages of alternative courses of action and reaching sums and totals that diverged from those advocating other approaches.

The committee concluded that the decisions that were made were affected by "environmental influences," which it described as political, ideological, organizational, and historical. The political factors were the successful lobbying of the Public Health Service by groups of gay men, who did not want homosexuality to be recognized as a risk factor for AIDS because of the stigmatization that could result, and by representatives of the fractionation industry, which did not want mandatory anti-HBc testing because of the cost. The ideological factor was an opposition to regulation by the federal executive. The organizational factors were the "[i]nteragency squabbling, lack of coordination, and miscommunication" between the Food and Drug Administration and the Centers for Disease Control, and the lack, in the blood products advisory committee of the Center for Biologics Evaluation, of the "social, ethical, political and economic expertise" that was needed to deal with issues such as "the risk of HIV transmissions versus the risk of further stigmatizing homosexuals." The historical factor was that, in 1976, the Centers for Disease Control had incorrectly predicted that an epidemic of swine flu would occur in the United States, an error that may have contributed to a lack of confidence on the part of the Food and Drug Administration

in the Centers' predictions about AIDS and to a lack of forcefulness in the Centers' presentation of its concerns. The committee completed its conclusions with the following remarks:

The Committee has not documented that any actions taken by decision-makers were inconsistent with their responsibilities, but does believe that decisionmakers chose the least risky course (to them) throughout the events as they unfolded. A good example of this is that blood and plasma collection organizations failed to undertake anti-HBc testing, and failed to recommend direct screening of homosexuals [direct questioning about the sexual orientation of male donors] in 1983.

More stringent donor screening activities were not implemented in 1983 because of the limited scientific information related to AIDS and the influence of political, economic, and regulatory forces with different agendas. The lack of adequate scientific knowledge prevented the key actors from making an accurate (or reasonable) risk-benefit analysis of proposals to change the blood donor selection process. As a result of these uncertainties and pressures from the blood industry and special interest groups, options that would have reduced HIV infection were not chosen, and policies that resulted in minimal change to the blood donor selection process were implemented. These policies not only provided a minimum of political risk to the blood banks and regulatory agencies in 1983, they also provided a minimum of protection from HIV for recipients of blood or blood products.

It is clear that the committee believed that the U.S. decision makers did not, as the committee thought they should have done, use epidemiological information – even if it amounted to less than conclusive scientific proof – as the basis for taking measures to reduce the risk of contamination of the blood supply.

The consequences in the United States of using concentrates made from pools of plasma

In 1994, a study entitled "HIV-1 Infection Incidence among Persons with Hemophilia in the United States and Western Europe, 1978–1990" was published in the *Journal of Acquired Immune Deficiency Syndromes*. The authors examined the incidence of HIV infection among hemophiliacs who had been treated at twelve treatment centres in the United States and four centres in Europe. From earlier studies conducted by others, the authors knew that some hemophiliacs had been infected with HIV as early as 1978. By performing HIV tests on preserved blood samples that had been taken from hemophiliacs over the course of many years at five of the twelve U.S. centres, the authors not only confirmed that infection had begun as early as 1978 but were able to determine the years in which many of the hemophiliacs treated at the five centres had first been infected.

The authors analysed data from the five centres about hemophiliacs who used large (more than 50,000 units per year) and moderate (20,000 to 50,000 units per year) amounts of factor VIII concentrate. They found that, by the beginning of 1981, more than 30 per cent of those patients had been infected with HIV. The proportion that had been infected rose steadily thereafter – by the beginning of 1982, to more than 50 per cent; by the beginning of 1983, to more than 80 per cent; by the summer of 1983, to more than 90 per cent; by the beginning of 1984, to more than 95 per cent. By the beginning of 1985, almost 100 per cent had been infected. By the time that AIDS was first reported in hemophiliacs in the summer of 1982, therefore, more than half the hemophiliacs who used large and moderate amounts of factor VIII concentrate had already been infected.

The authors also found that the rate of new infections among all hemophiliacs using factor VIII concentrate increased rapidly after 1978, was at its highest at the end of 1982, and then began to decline. They identified four possible reasons for the decline. One was the simple fact that, as more and more users of factor VIII concentrate were infected, there were progressively fewer users to become newly infected. The other three possible reasons were the recommendation of the National Hemophilia Foundation in December 1982 that hemophiliacs who had never used concentrate refrain from using it; the measures taken in early 1983 to reduce the risk of contamination for concentrate; and the use of heat-treated factor VIII concentrate, which began in the United States in May 1983 and was widespread there by the beginning of 1985.

By the spring of 1983, all U.S. plasma and blood centres had taken measures to reduce the number of contaminated units that were being collected. Because of the lapse in time between the collection of source plasma and whole blood and the regulatory release of the finished blood products, those measures would have had no effect on the quality of the factor concentrates being distributed until the autumn of 1983. By then, fewer than 10 per cent of the hemophiliacs who used large or moderate amounts of factor VIII concentrate were still uninfected. Despite the measures that were taken, almost all those persons became infected during the next fifteen months.

From the data from the five centres, the authors also made some findings about the rate of new infections among hemophiliacs who used factor IX concentrate. They found that, after some infections during the period 1978–80, the rate of new infections began to increase in 1981, was highest in late 1983, and then declined. The risk for hemophiliacs using factor IX concentrate was both lower and later than the risk for hemophiliacs using factor VIII concentrate.

The authors believed that it was “plausible to assume” that the statistics relating to the five centres were representative of the risk to all U.S. hemophiliacs. They noted that “the AIDS incidence curve and the distribution of

ages at AIDS onset in the cohort are similar to national trends derived from all AIDS cases among hemophiliacs reported to the United States Centers for Disease Control and Prevention."

The consequences in Canada of using concentrates made from pools of plasma

In 1982, Dr Christos Tsoukas began a study (the Montreal study) of immune abnormality among hemophiliacs. Dr Tsoukas was then an immunologist practising in Montreal, and later a member of the division of clinical immunology and the director of the immune deficiency treatment centre at the Montreal General Hospital and an associate professor of medicine and an associate director of the AIDS centre at McGill University. He enrolled thirty-four persons being treated in Montreal for severe type A hemophilia in the study and followed the progression of AIDS in this group. In 1984, he began another study (the multicentre study) of AIDS among 372 persons with bleeding disorders who were being treated at eleven centres in nine provinces. Of the 372 persons, 279 had type A hemophilia (175 severe, 53 moderate, and 51 mild), 49 had type B hemophilia (23 severe, 14 moderate, and 12 mild), and the remainder had other bleeding disorders.

In the multicentre study, Dr Tsoukas found that, of all type A hemophiliacs who had used cryoprecipitate exclusively, only 9 per cent had been infected with HIV; of those who had normally used cryoprecipitate but had also used some factor VIII concentrate, 50 per cent had been infected; of those who had normally used factor VIII concentrate, 84 per cent had been infected. The rate was highest – 91 per cent – among the severe type A hemophiliacs who had used factor VIII concentrate. Cryoprecipitate was not a concentrated product derived from plasma pools. Of the 41 type B hemophiliacs who used factor IX concentrate, two (5 per cent) were infected.

Unlike the U.S. study previously described, Dr Tsoukas's studies did not include retrospective analyses of stored blood samples from 1978 onward. Blood samples were taken and preserved in the Montreal study, however, beginning in 1982. All thirty-four persons enrolled in the Montreal study were treated with more than 40,000 units of factor VIII concentrate per year. Analysis of the preserved samples showed that twenty of the group (59 per cent) were already HIV positive in 1982 when the first blood samples were drawn, and all but one of them were HIV positive by 1984. These percentages are consistent with the statistics from the U.S. study for severe hemophiliacs using large and moderate amounts of factor VIII concentrate.

In his multicentre study, Dr Tsoukas found that, of the 193 persons who were HIV positive, 174 (90 per cent) were already HIV positive at the beginning of the study in 1984. This result, too, is consistent with the U.S. study.

Commentary

The relative risks of U.S. and Canadian concentrates

With respect to the factor concentrates that were made from plasma collected between 1978 and 1982, there is no doubt that Canada's dependence on commercial concentrates made from U.S. plasma increased the risk that Canadians with hemophilia would be infected with HIV. The onset of the AIDS epidemic occurred earlier in the United States than in Canada. Moreover, the U.S. practice of paying persons for their plasma increased the risk that persons in the high-risk groups would offer their plasma because they needed money. The U.S. practice of collecting plasma in prisons also increased the risk. The plasma collected in the United States and used in commercial concentrates was therefore more likely to be contaminated than that collected in Canada by the Red Cross from volunteers.

Before the Red Cross began to distribute factor VIII concentrate in 1979, it took steps to increase the amount of Canadian fresh frozen plasma in order to minimize its predicted dependence on commercial products. It began to move its blood collection clinics closer to the blood centres, so that the plasma recovered from the whole blood could be fresh frozen to preserve its factor VIII activity. After a successful pilot project, it also began to collect source plasma regularly through plasmapheresis in 1979, and it requested annual budget increases to allow it to expand its plasmapheresis program. Financially supporting the expansion of the plasmapheresis program would have promoted the principle of self-sufficiency in blood products adopted by the federal and provincial governments in 1976. However, from 1979 until the threat of AIDS to hemophiliacs became known in 1982, the Red Cross's requests for annual increases to expand the plasmapheresis program were accepted only in part by the government officials who reviewed them. It is now known that, if the plasmapheresis program had been expanded and the dependence on commercial concentrates until 1983 had been reduced, the risk of AIDS to hemophiliacs using factor concentrates would have been reduced.

It is more difficult to compare the risks in using factor VIII concentrate that was made from U.S. and Canadian plasma collected during 1983 and 1984, after measures were taken to screen donors. On the one hand, the AIDS epidemic continued to be more advanced in the United States than in Canada, and the U.S. practice of paying persons for their plasma continued. On the other hand, the screening measures used in the United States were more likely to identify and defer persons at high risk of contracting AIDS than those used by the Red Cross in Canada. Moreover, the U.S. fractionators stopped using U.S. plasma that was collected in prisons and in high-risk areas. It cannot be said whether, in plasma collected during 1983 and 1984, the risk associated with the commercial concentrates that were made by the U.S. fractionators was higher or lower than that associated with custom-fractionated concentrates made exclusively from Canadian volunteer donations. It is obvious, however, from the rates of infection among the users of

factor VIII concentrate in both the United States and Canada that the risks associated with both the commercial and custom-fractionated factor VIII concentrates were high.

Many of the lots of commercial factor VIII concentrate made by Connaught during 1983 and 1984 contained plasma that came from prisons and the Irwin Memorial Blood Bank. Those lots had a higher risk associated with them than would have been the case if plasma from those sources had not been used.

It is possible to estimate the risk that the custom-fractionated factor VIII concentrate distributed by the Red Cross contained plasma from persons infected with HIV. Dr Robert S. Remis, an epidemiologist, formerly the director of the regional bureau of infectious diseases in Montreal and now a consulting epidemiologist with the AIDS bureau of the Ontario Ministry of Health and an associate professor in the department of public health sciences of the Faculty of Medicine at the University of Toronto, has conducted a number of retrospective studies of HIV infection through the transfusion of blood components. One of his studies was done for the Laboratory Centre for Disease Control and others were done for the purpose of the Inquiry, and they were summarized by Dr Remis at the hearings. In the study for the Laboratory Centre, Dr Remis estimates the rate of HIV contamination associated with blood components, year by year, from 1978 to 1984. Using Dr Remis's estimates and the standard equation described earlier in this chapter, it is possible to calculate the approximate risk of HIV contamination in the custom-fractionated factor VIII concentrate that was produced from fresh frozen plasma recovered from whole blood donated in those years. Dr Remis's estimates of prevalence and the risks calculated using the equation are set out in Table 14.6. The risk associated with Connaught's custom-fractionated concentrate was lower than the risk with Cutter's custom-fractionated concentrate because Connaught used smaller pools of plasma in the manufacture of its factor VIII concentrate.

During 1983–4, the Red Cross and others said that the risk of acquiring AIDS from a transfusion in Canada was one or two in a million. For that risk to be possible, there had to be at least one infected donor. If the standard equation, which was known and in use at the time, had been used to estimate the risk in custom-fractionated concentrates if only one donor were infected, the calculation would have produced an estimated risk of approximately 1 per cent (in concentrates produced by Connaught) and 3 per cent (in concentrates produced by Cutter), and it would have been immediately apparent that the risk in the concentrates was much higher than the risk in blood components.

The risk of infection to any individual hemophiliac might have been lower or higher than the risks of contamination shown in Table 14.6. On the one hand, it cannot be assumed that every vial of concentrate from every contaminated lot caused infection when used. Some lots, although contaminated,

Table 14.6

Prevalence of HIV infection for persons donating whole blood to the Canadian Red Cross Society, 1978–84, and estimated risk of contamination in lots of factor VIII custom-fractionated concentrate made from plasma recovered from that blood (per cent)

Year of collection	Prevalence of HIV infection	Risk of contamination for factor VIII concentrate (custom fractionated)	
		from Cutter	from Connaught
1978	0.001	18	7
1979	0.001	18	7
1980	0.002	33	14
1981	0.004	55	26
1982	0.010	86	53
1983	0.014	94	65
1984	0.025	97	74

Source for rate of contamination: R.S. Remis and R. Palmer, "The Epidemiology of transfusion-associated HIV infection in Canada, 1978–1985" (unpublished, 1994)

Risk calculated using the standard formula for that operation: probability that the pool contains a blood-borne pathogen = $1 - (1 - p)^n$, where p = the prevalence of infection in the population of donors and n = the number of contributors to the plasma pool. Over these years, plasma pools at Cutter averaged 20,000 units and at Connaught, 7,500 units.

may not have caused infection because the amount of virus in the pool was low and was destroyed during the processing of the concentrate. And, for reasons that are not entirely clear, some persons might have been infected with concentrate from a lot while others were not. For these reasons, the risk to a hemophiliac might have been lower than those in the table. On the other hand, for a hemophiliac who infused concentrate from more than one lot per year, the risk of exposure to at least one contaminated lot was higher than the risk of contamination shown in Table 14.6. Almost all severe type A hemophiliacs infused factor VIII concentrate from more than one lot every year, and it was not unusual for them to infuse concentrate from five or more lots. Table 14.7 shows the cumulative risk.

No one at the Red Cross or the Health Protection Branch tried to calculate the risk associated with factor concentrates based on the assumption that one donor was infected with the agent causing AIDS. On more than one occasion, the Red Cross stated that concentrates were safer than cryoprecipitate. The basis for the statement was the assumption that the causative

Table 14.7
Estimated cumulative risk per year of exposure for a hemophiliac
infusing concentrate from multiple lots (per cent)

Year of collection	Risk of contamination per lot	Number of lots infused			
		1	2	5	10
<i>Connaught custom-fractionated factor VIII concentrate</i>					
1978	7	7	14	30	52
1979	7	7	14	30	52
1980	14	14	26	53	78
1981	26	26	45	78	95
1982	53	53	78	98	100
1983	65	65	88	99	100
1984	74	74	93	100	100
<i>Cutter custom-fractionated factor VIII concentrate</i>					
1978	18	18	33	63	86
1979	18	18	33	63	86
1980	33	33	55	86	98
1981	55	55	80	98	100
1982	86	86	98	100	100
1983	94	94	100	100	100
1984	97	97	100	100	100

Risk calculated using the standard formula for that operation: cumulative risk = $1 - (1 - r)^n$, where r = the risk of a single treatment and n = the number of independent infusions

agent of AIDS, if it was present in a unit of plasma, would be so diluted in the plasma pool that the concentrates made from it would not be infectious. There was no scientific justification for this assumption. It was known not to be true of hepatitis B, a disease that infected most hemophiliacs who used concentrates. Until HIV was discovered, there was no way of knowing the amount of virus in a contaminated plasma unit and whether it would be diluted to the extent that the concentrates would not be infectious.

Rather than calculate the risk, both the Red Cross and the Health Protection Branch relied on the low number of reported AIDS cases among Canadian hemophiliacs and said that there was no proven link between the use of concentrates and AIDS. In March 1984, the Laboratory Centre for Disease

Control published a Supplement on AIDS in its *Canada Diseases Weekly Report*. The text, written by the National Advisory Committee on AIDS, included a discussion of blood and blood products that was drafted by the Red Cross. It said that "the chances of developing AIDS from a blood transfusion are approximately 2 in a million." About the risk associated with concentrates, it said:

Plasma derivatives associated with the development of AIDS are Factor VIII concentrate – the anti-hemophilic factor (AHF) – and Factor IX complex which are used in the treatment of hemophilia. Small-pool products (cryo-precipitate) expose patients to smaller numbers of donors than large-pool concentrates (Factor VIII and Factor IX), resulting in a lower theoretical risk of exposure to causal "agents."

As of February 1984, 21 cases of AIDS in hemophilia patients have been reported in the US and 2 in Canada. To date, there is no conclusive evidence directly linking the development of AIDS to Factor VIII concentrate or Factor IX complex utilization. Some increased risk appears to be related to annual utilization of more than 50,000 units of AHF. Medical/Scientific Advisory groups associated with the Canadian Hemophilia Society and the National Hemophilia Foundation in the US have issued specific recommendations for managing hemophilia patients receiving blood and blood products.

Reliance on the number of reported cases of AIDS for hemophiliacs led to the risk of hemophiliacs being seriously underestimated. AIDS was known to have a latency period following infection. An appropriate risk analysis was one that focused on the risk of contamination of the plasma pools and recognized that, because of the latency period, the number of reported cases of AIDS was only a fraction of the number of persons infected; it was also one that calculated the risk associated with the concentrates on the basis of an estimate of the number of donors who were infected, and that calculated the risk of exposure to hemophiliacs who infused concentrates from multiple lots. If such an assessment had been made, and if its results had been made public, hemophiliacs and their physicians would have been made aware of the magnitude of the risk associated with using concentrates.

On 4 July 1985, at a federal-provincial conference on AIDS, Dr Davey, the assistant national director of the Red Cross's blood transfusion service, said that, if heat-treated concentrates (which had a risk of contamination that was close to zero) had been available five years earlier (that is, in the summer of 1980), only three cases of AIDS would have been prevented among Canadian hemophiliacs. His estimate was not consistent with an assessment of risk based on the nature of pooled plasma products.

The importance of the measures taken to reduce the risk

Despite the high rate of infection among severe hemophiliacs by 1983, and the high risk of contamination in factor concentrates, the measures that were taken to reduce the number of contaminated plasma units were not useless. Any measure that reduced the number of contaminated plasma units, even slightly, reduced the risk of contamination in the concentrates. For hemophiliacs who were still uninfected in the autumn of 1983, the measures that were, and were not, taken were crucial. They were crucial especially for hemophiliacs who seldom used factor concentrates – most of the mild and moderate hemophiliacs, and the severe hemophiliacs (especially children) who used cryoprecipitate or fresh frozen plasma in their factor replacement therapy – and whose risk of infection might be confined to the risk in a single lot.

If measures as comprehensive as those adopted in the United States had been taken in Canada to exclude donations from persons at high risk of contracting AIDS, the risk of AIDS to hemophiliacs using custom-fractionated factor VIII concentrate would have been reduced. The Red Cross, instead, relied on donors to refrain voluntarily from donating blood or plasma if they belonged to a high-risk group. The Bureau of Biologics did not require the Red Cross to take measures to exclude donations from persons at high risk. Moreover, the Red Cross did not take, and the bureau did not require, special measures to screen plasmapheresis donors for AIDS, despite the increased danger of contamination arising from the fact that one infected person could give approximately twenty-five donations through plasmapheresis in a year.

The Bureau of Biologics licensed all the factor concentrates that were distributed in Canada. The bureau had the authority to require that the manufacturers of those concentrates meet certain conditions. It could have required them to ensure that measures had been taken to reduce the risk of contamination with AIDS in all the plasma they used, including that collected by the Red Cross. In these circumstances, if the Red Cross had not introduced the risk-reduction measures, its plasma could not have been fractionated. Specifically, the bureau could have required the manufacturers to ensure that the following measures had been taken: that the persons from whom whole blood and plasma were collected were told what groups were at high risk of contracting AIDS; that they were told the symptoms of AIDS; that they were asked if they belonged to one of the high-risk groups or had any of the symptoms of AIDS; that they were told that they could not donate blood or plasma if they belonged to one of the high-risk groups or had any of the symptoms; and that whole blood and plasma were tested for the presence of anti-HBc. The bureau did not exercise that authority.

Another measure that could have been taken was to reduce the size of the plasma pools. The numbers in Table 14.1 demonstrate the effect on risk of reducing the size of the pools. The bureau did not require that factor concentrates be made from smaller pools of plasma.

Encouragement of alternative methods of treatment

Until the causative agent of AIDS was identified and a means was found to inactivate it without destroying the activity of the factor VIII and factor IX in concentrates, the only way to avoid the substantial risks inherent in these products was not to use them. Cryoprecipitate and fresh frozen plasma are blood components that can be used instead of factor VIII and factor IX concentrates, respectively. The risk from them, while not insignificant, remained hundreds to thousands of times lower than the risk from concentrates. Only a few physicians treating hemophiliacs strongly encouraged their patients to use them rather than concentrates.

In Calgary, physicians at the comprehensive-care centre did advise their patients to use cryoprecipitate and fresh frozen plasma instead of factor concentrates from the time that concentrates became available in Canada. They did so at first as a safeguard against infection with hepatitis and, later, with AIDS. They were supported in their advice by the medical directors of the Red Cross's Calgary blood centre and members of the local hemophilia organization. The results of that advice were substantial. In his multicentre study, Dr Tsoukas found that the rate of HIV infection among persons treated at the Calgary centre was 20 per cent, compared with rates at the other ten participating centres of 50 to 80 per cent.

From mid-1982, there was a growing recognition that AIDS could be transmitted through factor concentrates. The Bureau of Biologics, whose standard for licensing was that a product be "not unsafe," was not unreasonable in not revoking the licences it had issued for factor concentrates. Until heat-treated concentrates were obtained, there were some hemophiliacs for whom cryoprecipitate or plasma were not always therapeutic options and for whom concentrates were necessary. In every such case, the physician had to weigh the risk of contracting AIDS through the use of a concentrate against the risk of death or significant morbidity if a concentrate were not used, to tell the patient of the respective risks, and to give the patient the opportunity to make an informed decision about the appropriate treatment.

In March 1983, the medical and scientific advisory committee of the Canadian Hemophilia Society recommended that cryoprecipitate, rather than concentrates, be used to treat persons with type A hemophilia who had never before been treated with concentrate. The committee expressly recognized that "for most patients, lyophilized [freeze-dried] concentrates will still be the only feasible therapeutic modality." The recommendation had an effect. After several years of reduced consumption, the use of cryoprecipitate increased 16 per cent in 1983 and an additional 17 per cent in 1984. Still, the majority of persons with severe type A hemophilia continued to use factor VIII concentrate for routine therapy, and the use of those concentrates increased 5 per cent in 1983 and an additional 4 per cent in 1984. The Bureau of Biologics knew about the advisory committee's erroneous recommendation. It believed,

however, that the recommendation applied to the treatment of all hemophiliacs, and therefore that cryoprecipitate had been recommended for use by all hemophiliacs, especially for those with mild cases of type A hemophilia. The fact that the number of lots the bureau released for distribution did not decline gave rise to the inference, one the bureau did not draw, that the majority of type A hemophiliacs were continuing to use factor VIII concentrate for routine treatment.

During 1982, it was reported that some hemophiliacs in the United States who were using factor concentrates were developing AIDS. In December of that year, the four U.S. fractionators agreed to introduce measures intended to reduce the recognized, if not yet quantified, risk of AIDS inherent in the use of the concentrates then available. There was by then enough information to justify the inclusion of a warning about AIDS in the product inserts for factor concentrates. Such warnings were not included in the product inserts until the autumn of 1983 and early 1984, and then only by the U.S. fractionators for the commercial concentrates made from U.S. plasma.

The Red Cross could have required that the product inserts accompanying the factor concentrates that it distributed in Canada include warnings. Instead, in early 1984, when Cutter offered to include a warning in the inserts for the custom-fractionated concentrates it was making from Canadian plasma, the Red Cross declined the offer. For its part, the Bureau of Biologics did not require that the product inserts include a warning. Such a warning could have alerted the physicians treating hemophiliacs to the importance of assessing the respective risks of continuing or stopping therapy with factor concentrates every time they were used. The ability of physicians to assess those risks, and to advise their patients about the alternatives, depended on the physicians' full understanding of the risk of AIDS in the use of concentrates. It was not reasonable to assume that, in the absence of such a notice in the product inserts, all physicians prescribing factor concentrates – and all hemophiliacs using them – would be aware of the inherent risk of HIV infection.

The use of purchased plasma

The fractionation of plasma purchased by a fractionator from collecting centres outside its own organization causes a problem for the fractionator. Unless the plasma is collected under contract by a small number of plasma centres, it is difficult for a fractionator to ensure that the plasma received is safe. This is especially true when the plasma passes through the hands of one or more brokers who are gathering plasma from many sources that are not identified sufficiently in advance of delivery to allow the manufacturers to conduct inspections. This problem is amply illustrated by Connaught's experience.

For the regulator, an additional problem arises when the plasma used for fractionation comes from collections made outside the country. Within Canada, beginning in 1979, the Bureau of Biologics licensed all plasmapheresis centres,

but it inspected them only sporadically. It did not license the Red Cross's blood centres until 1989. Outside the country, the bureau did not license blood and plasmapheresis centres, and it was impossible for the bureau to inspect all blood and plasmapheresis centres collecting plasma that might be used in a blood product distributed in Canada. Indeed, licences were not required and inspections were not conducted by the Food and Drug Administration for most of the U.S. blood centres that sold recovered plasma to the fractionators. As a result, commercial concentrates distributed by the Red Cross contained some recovered plasma that came from blood centres that were licensed and inspected by neither the U.S. nor the Canadian regulator.

When the regulation of plasma collection in another country is left to that country's regulatory authorities, the possibility arises that the regulator, fractionator, and distributor will be unaware of important decisions about the ways in which the plasma is collected. This is what occurred when the four U.S. fractionators, at their informal meeting with the Food and Drug Administration in December 1982, agreed not to use plasma from high-risk sources. Connaught, without knowing it, became the only fractionator in North America that was using plasma collected in prisons and in the high-risk areas identified by the Food and Drug Administration. The Red Cross and the Bureau of Biologics were equally unaware that the use of plasma from those sources was no longer acceptable to the U.S. regulatory authorities.

The use of plasma obtained through brokers leads to another cause for concern. Information about plasma follows the same route as the plasma itself. If some problem is found in a unit of plasma after it enters the system, any one of the organizations that has held that unit may decide that the problem is not significant enough to report to the next link in the supply chain, whether that link is another organization or the eventual user. The more organizations that are involved in the collection, sale, and distribution of plasma, the more likely it is that the chain of communication will be broken. As a result, a fractionator might not be given the opportunity to decide whether to withdraw or recall a product lot in circumstances in which it would otherwise do so. This is what occurred in June 1983 when Continental Pharma decided that the plasma collected from the Grady prison did not pose a significant health risk and, therefore, it did not inform Connaught about the problem. Had the information been given to Connaught in June, hundreds of additional vials from the lots could have been retrieved before they were used.

The need for independent judgment

Connaught learned in late 1984 that it had made factor VIII concentrate from pools contaminated with plasma collected by Irwin Memorial from persons with AIDS. By early January 1985, Connaught had determined which lots were affected, and informed both the Red Cross and the Bureau of Biologics. One of the lots was not to expire until the end of January 1985. Consultation

occurred among the three organizations. It was acknowledged that some of the vials from the lot that had not expired could still be in the home supply of hemophiliacs. In mid-January a decision was made not to recall or withdraw the lots in question. At the hearings, witnesses from each of Connaught, the Red Cross, and the bureau suggested that the decision not to recall or withdraw the lots was made by the other two organizations.

The manufacturer of a blood product, the distributor of a blood product, and the regulator must make independent judgments when there is reason to believe that a product that has been distributed may be unsafe. When Connaught, the Red Cross, and the bureau learned of the contamination, each organization, independent of the others, should have considered what action was required. This is not to say that consultation should not have taken place, but that, after consultation, each should have decided whether a recall or a withdrawal should take place. If any of the three organizations had been required to exercise independent judgment, only one decision would have been possible – that a recall take place.

The Conversion to Heat-Treated Concentrates

At the end of September 1984, the British medical journal *The Lancet* reported that heat treatment of factor VIII concentrate could inactivate retroviruses. One month later, the Centers for Disease Control in Atlanta reported that heat treatment inactivated the human immunodeficiency virus (HIV). In mid-November 1984, the Bureau of Biologics, the federal agency regulating blood products in Canada, recommended that the Canadian Red Cross Society (Red Cross) and the fractionators supplying it with coagulation factor concentrates replace non-heat-treated concentrates with heat-treated concentrates "as soon as possible." At the beginning of May 1985, the Red Cross began limited distribution of heat-treated concentrates for use by some hemophiliacs, and at the beginning of July 1985 it began general distribution of heat-treated concentrates for use by all hemophiliacs in Canada. The conversion to heat-treated concentrates was an important event. Before the introduction of heat-treated concentrates, some 800 Canadian hemophiliacs had been infected with HIV through the blood products on which their health depended. Thereafter, very few were infected.

This chapter describes the decisions that were reached and the actions that were taken during the months that intervened between the publication of the reports on viral inactivation by heat treatment and the general distribution of heat-treated concentrates in Canada. The main issue reviewed is whether the Red Cross, the Bureau of Biologics (part of the Health Protection Branch of the Department of National Health and Welfare), the Canadian Blood Committee, and the Canadian Hemophilia Society and its medical and scientific advisory committee acted to bring about conversion to heat-treated concentrates as soon as possible.

The discussion and the eventual decisions that led to the conversion to heat-treated products focused on factor VIII concentrate, used to treat type A hemophilia. The timeliness of conversion to heat-treated factor IX concentrate, used to treat type B hemophilia, was equally important, because many persons with type B hemophilia were infected with HIV through factor IX concentrate that had not been heat treated. The status of factor IX concentrate, however, was often only implicit or ignored in the decision making. The implementation of conversion to heat-treated factor IX concentrate is reviewed separately.

Evidence of the transmission of AIDS through concentrates

The epidemiological evidence that factor concentrates could transmit the yet-to-be-discovered causative agent of AIDS began to accumulate in 1982. By the summer of 1983, it was recognized that there was a risk that almost every lot of U.S. concentrate made from purchased plasma could be contaminated. In July of that year, the subject was discussed at a meeting of the blood products advisory committee, a standing committee of the Center for Biologics Evaluation and Research that advised the U.S. Secretary of Health, the assistant secretary of health, and the commissioner of the Food and Drug Administration. At that meeting, Dr John Petricciani, the director of the U.S. Office of Biologics, the body regulating the U.S. blood system, said that "it is apparent that some donors to plasma pools have been, or will be, AIDS victims." Dr Michael Rodell, the vice-president (regulatory and technical affairs) of the Armour Pharmaceutical Company (Armour), one of the four U.S. commercial fractionators, and a representative of the Pharmaceutical Manufacturers Association, said that, given the size of the plasma pools from which commercial concentrates were made and the frequency with which persons paid for this plasma gave through plasmapheresis, it was statistically possible for as few as four infected persons to contaminate the entire world supply of factor VIII concentrate. Dr Rodell's analysis was confined to U.S. commercially produced concentrates made from persons paid for their plasma, but no one who heard him could have missed the implication that, for any given lot, the use of concentrates carried a significant risk of exposure to an AIDS-causing agent. Dr John Derrick, the internal adviser on regulatory affairs and good manufacturing practices for the Canadian Red Cross Society's blood transfusion service, attended the meeting at which Dr Rodell spoke and recorded his statement.

In the summer of 1984, the epidemiological evidence linking the use of factor concentrates to HIV infection and the development of AIDS was persuasive. In an article published in the *Canadian Medical Association Journal* on 1 July 1984, Dr Derrick recognized this link: "Recent epidemiological reports from the United States leave little reason to doubt that the acquired immune deficiency syndrome (AIDS) can occur as an outcome of receiving blood components or plasma-derived coagulation factor concentrates." In the same article, he reported that the rate of AIDS among hemophiliacs in the United States and Canada was already approximately two per thousand, but that it would take time to determine the final rate "since the period between exposure [to HIV] and diagnosis of the syndrome is ... usually greater than two years."

Roughly three months later, in its issue of 29 September 1984, *The Lancet* published a "preliminary communication" by Dr Jay A. Levy, a professor at the University of California at Berkeley, and colleagues that reported that retroviruses in factor VIII concentrate could be inactivated through heat treatment. The Levy article began a series of events that culminated in the conversion from non-heat-treated to heat-treated concentrates.

October 1984: The Red Cross's view of the benefits of heat treatment

On 28 September 1984, the day before the publication of the Levy article in *The Lancet*, Dr Derek Naylor submitted an article to *Hemophilia Today*, a publication of the Ontario chapter of the Canadian Hemophilia Society. As the director of blood products services in the blood transfusion service, Dr Naylor was the senior Red Cross official whose sole responsibility was for blood products, including factor concentrates. He wrote in the article:

There is ... some evidence to suggest that infection with HTLV-III virus [HIV], commonly believed to be the causative agent of acquired immunodeficiency syndrome (AIDS), is associated with the use of coagulation factor products.

But, he continued,

[c]ompared to the established link between coagulation factor therapy and hepatitis, there is much less evidence that coagulation therapy carries a significant direct risk of AIDS.

Regarding safety gains from heat treatment, he added,

[w]hile heat-treated products are presumed by some to offer certain theoretical advantages, the data are insufficient at this time to assess their efficacy or to recommend that the presently licensed heat-treated products be used instead of the standard coagulation factor products.

Dr Naylor's view, that there was "some evidence to suggest" a link between the use of concentrates and infection with AIDS, was not necessarily inconsistent with the view expressed by Dr Derrick three months earlier in the *Canadian Medical Association Journal* that there could be "little reason to doubt" such a link. It is possible to have much less evidence regarding one type of infection (HIV) compared with another (hepatitis) and still have little reason to doubt a connection between the use of concentrates and the first type of infection. However, the manner in which Dr Naylor and Dr Derrick expressed their respective views conveyed different meanings. A reader would have reasonably inferred from Dr Naylor's article that HIV infection from concentrates was only a possibility and might not occur at all; the same reader would have reasonably inferred from Dr Derrick's article that HIV infection from concentrates, while not yet fully proven, quite probably did occur. Moreover, it would be reasonable to conclude from Dr Naylor's position that, since HIV transmission from concentrates was only a possibility, there was no sound

reason for converting to heat-treated concentrates – a point of view reinforced by his express statement that there was not yet conclusive data that heat treatment was effective.

A copy of the draft article for *Hemophilia Today* was sent to Dr Man-Chiu Poon, a physician who treated hemophiliacs and who was also a deputy medical director of the Red Cross's Calgary blood centre. On 15 October, he wrote to Dr Naylor urging him to reconsider his position.

During his training in the treatment of hemophilia in the 1970s, Dr Poon had developed a preference for cryoprecipitate in treating type A hemophilia because the rate of hepatitis infection was lower when cryoprecipitate was used than when factor VIII concentrate was used. He had also developed a heightened sense of the general risk of transmission of diseases through concentrates. After his training, he had worked at a clinic in Alabama where many hemophiliacs were already using concentrates when he arrived, in part because concentrates cost less than cryoprecipitate. In 1982, one of his patients developed AIDS, the fourth hemophiliac in the United States reported to have done so. From 1982 through 1984, Dr Poon was in regular communication with the Centers for Disease Control in Atlanta, and in particular with Dr Bruce Evatt, the centers' principal physician concerned with the epidemiological connection between blood products and AIDS.

In his letter to Dr Naylor, Dr Poon said he had just visited the Centers for Disease Control. While there he had spoken to Dr Evatt and Dr J.S. McDougal. Dr McDougal, a scientist, had developed an assay capable of detecting small amounts of HIV and was using that assay to conduct studies on the inactivation of HIV in factor VIII concentrate by heat treatment. Dr Evatt told Dr Poon that the medical and scientific advisory council of the U.S. National Hemophilia Foundation had recommended the use of heat-treated concentrates by all hemophiliacs, and that this recommendation (made on 13 October, that prescribing physicians "strongly consider changing to heat-treated products with the understanding that the protection against AIDS is yet to be proven") would be published in the centers' *Morbidity and Mortality Weekly Report*. Dr McDougal had told Dr Poon that HIV could be inactivated through heat treatment with little loss of factor VIII activity. Dr Poon wrote to Dr Naylor:

The reason I dictated this letter right after my visit [to the Centers for Disease Control] is to alert you of the above developments and to urge you to look into this very carefully and objectively. You should perhaps talk to Dr Evatt at the Atlanta CDC [Centers for Disease Control] in person. I anticipate that once the official recommendation has been disseminated, especially when it has been published in the *MMWR*, a great deal of pressure will be put on the hemophilia treatment centres as well as the Canadian Red Cross Blood Transfusion Service from the Canadian hemophiliacs for provision of heat-treated concentrates.

It is clear from his letter and from his testimony that Dr Poon's purpose in writing was to overcome what he perceived to be the Red Cross's resistance to converting to heat-treated factor concentrates.

Dr Poon's letter did not reach Dr Naylor until 24 October. Two days later, Dr Naylor, with Dr Derrick's help, revised the article he had submitted to *Hemophilia Today*. The changes in the key sentences quoted above are emphasized in the following extracts from the revision.

There is ... some evidence to suggest that infection with HTLV-III virus [HIV], commonly believed to be the causative agent of acquired immunodeficiency syndrome (AIDS), is associated with the use of coagulation factor products ...

Compared to the established link between coagulation factor therapy and hepatitis, *evidence that coagulation factor therapy carries a significant direct risk of AIDS is considerably less conclusive* ...

While heat-treated products can be presumed to offer certain theoretical advantages, *the information as to their efficacy and the absence of possible other side effects is still inconclusive*.

These revisions did not change the main sense of the article, which still left serious doubt about the need for conversion to heat-treated concentrates.

Three days later, on 29 October, Dr Naylor and Dr Derrick reported to Dr Roger Perrault, the national director of the Red Cross blood transfusion service, that they had recalled the original version of the article submitted to *Hemophilia Today* because of new information. They attached to their memorandum copies of the revised article, Dr Poon's letter, and the Levy article. In the memorandum itself, they said that "the retrovirus(es) LAV/HTLV-III [HIV], while strongly associated with the incidence and development of AIDS, have yet to be definitively demonstrated as its cause." They then expressed an opinion that was new within the national office of the blood transfusion service: "[A] heat treatment procedure for factor VIII concentrate which effectively inactivates retroviruses without significantly affecting the potency of the product is now available." No such statement was included in the revised article, which was submitted to and published by *Hemophilia Today* without further change.

October–November 1984: The desire for a reserve inventory

To maintain adequate stocks of fractionated blood products for an entire country was no easy matter. The Red Cross had experienced shortages of factor VIII concentrate throughout 1983 and 1984, and on some occasions had come within a few days of running out, but had always been able to supply what was needed for non-elective treatment. Fractionated blood products, including factor VIII and factor IX concentrates, were purchased from the manufacturers

through the national office of the blood transfusion service. They were then distributed to the service's seventeen blood centres, which in turn distributed them to local hospitals, hemophilia clinics, and in rare circumstances direct to hemophiliacs. Local supply thus depended upon national purchasing.

The national office had three ways of obtaining fractionated blood products generally and factor concentrates in particular. In order of descending preference, determined by cost and a preference for all-volunteer Canadian plasma, these methods were *custom fractionation* of plasma collected by the Red Cross; *supplementary purchases* of large quantities of commercial products, usually made from plasma obtained from persons who had been paid, and pursuant to a contract that was usually for a one-year period; and *spot purchases* of smaller quantities of commercial products from a fractionator for delivery as soon as possible.

Every autumn, an assistant of Dr Naylor estimated the demand for factor VIII concentrate during the next year, the volume that could be produced from plasma collected in Canada by the Red Cross, and, from those figures, the quantity made from plasma collected elsewhere that would have to be purchased from commercial fractionators. The assistant's estimates for 1985 were set out in a memorandum dated 4 October 1984. In it, he recommended that the blood transfusion service buy enough commercially produced factor VIII concentrate to meet the demand and, in addition, establish a two-to three-month reserve inventory to eliminate the chronic shortages that the Red Cross had been experiencing.

On 30 October, Kenneth Poyser, who represented the Canadian Hemophilia Society on the advisory subcommittee of the Canadian Blood Committee, raised the issue of factor concentrate shortages at a meeting of that body. He moved, seconded by Dr Perrault, that the subcommittee recommend the accumulation of a reserve inventory of factor VIII and factor IX concentrates of three months or more. The motion was carried.

In a telexed message to Dr Perrault dated 8 November 1984, Dr Denise Leclerc-Chevalier, the executive director of the Canadian Blood Committee, reported that she had consulted her executive committee about the issue and that it had decided that "the BTS [blood transfusion service] national office should take appropriate action to purchase additional factor VIII to satisfy the needs of the Canadian population and to keep the inventory at an acceptable level." Hand-written notes, also dated 8 November, on the Red Cross's copy of the telex record that this action was "in progress" and that the "acceptable level" of factor VIII inventory had been "defined as 'three months or more'" by the advisory subcommittee, subject to the agreement of the Canadian Blood Committee. Dr Leclerc-Chevalier's telexed message conveyed the committee's agreement.

On 13 November, Dr Perrault wrote a memorandum to file that recorded the contents of Dr Leclerc-Chevalier's telexed message and the hand-written notes as follows:

A telex has been received from Dr Leclerc-Chevalier indicating that an *acceptable* level of inventory for factor VIII concentrate be held by the Red Cross. It was established [at] the meeting of October 30 [of the advisory subcommittee] that such an acceptable level is three months or more. [Emphasis in original.]

Copies of Dr Perrault's memorandum were sent to Dr Leclerc-Chevalier and, within the Red Cross, to Dr Martin Davey (the assistant national director of the blood transfusion service), Dr Derrick, Dr Naylor, Dr Naylor's assistant, and Claude Morin, the national administrator of the blood transfusion service, who was in charge of the service's finances, including its fractionation account, the money the Red Cross held in trust for the provinces to pay fractionation-related expenses. The recipients of the memorandum included all the persons in the national office of the blood transfusion service who were concerned with factor concentrates and the person at the Canadian Blood Committee to whom the service reported purchases of blood products.

On 9 November 1984, one day after the agreement of the Canadian Blood Committee was conveyed by Dr Leclerc-Chevalier and four days before Dr Perrault's memorandum was written, Dr Davey received advance notice from Dr Wark Boucher, the chief of the blood products division of the Bureau of Biologics, that the bureau was going to recommend conversion to heat-treated concentrates. In his memorandum to file recording this information, Dr Davey wrote:

I told him [Dr Boucher] that CRC [Canadian Red Cross] will be holding up to three months supply of factor VIII, plus some in process, and he agreed that the new policy will not prevent use of this material. BPS [blood products services] are endeavouring to secure a three month inventory at present.

Hyland and Cutter heat-treated products are now licensed in Canada. It is understood that Armour has a submission in process.

Hyland and Cutter were U.S. fractionators, the Hyland Therapeutics Division of Travenol Laboratories Inc. and the Cutter Biological Division of Miles Laboratories Inc.

16 November 1984: The directives of the Bureau of Biologics for conversion "as soon as possible"

On 16 November, the Bureau of Biologics issued two directives. The Red Cross was told:

Because heat treatment of antihemophilic factor, human, dried (AHF) products has been shown to inactivate some viral agents that may cause serious disease, further reliance on AHF products that have not been heat treated cannot be justified.

The Bureau of Biologics therefore recommends that use of untreated AHF be replaced as soon as possible with AHF products that have been heat treated.

The manufacturers were told:

Because heat treatment of antihemophilic factor, human, dried (AHF) has been shown to inactivate some viral agents that may cause serious disease, we have informed the Canadian Red Cross that further reliance on AHF products that have not been heat treated cannot be justified and that such products should be replaced with heat-treated AHF as soon as feasible.

The decision to make the recommendations in these directives was reached jointly by the bureau's director, Dr John Furesz, its assistant director, Dr David Pope, and Dr Boucher after the publication of the results of Dr McDougal's studies by the Centers for Disease Control. Although the two directives contained somewhat different wording for the time of conversion, "as soon as possible" and "as soon as feasible," the bureau intended no difference in meaning. And, although the directive to the Red Cross "recommends" conversion, the clear intent of both directives was to require that conversion take place.

November–December 1984: Red Cross inquiries regarding the availability of heat-treated product

By the end of November 1984, all four U.S. fractionators had been licensed to distribute heat-treated factor VIII concentrate by the U.S. Food and Drug Administration. Hyland had been licensed in March 1983; Armour, in January 1984; Alpha Therapeutic Corporation (Alpha), in February 1984; and Cutter, in January 1984 for a wet process (in which heat was applied to the liquid pool of plasma) and in February 1984 for a dry process (in which heat was applied to the freeze-dried concentrate). Two of the U.S. fractionators had received Canadian licences: Hyland, in November 1983; and Cutter, for its dry process, on 13 November 1984. As a result, Hyland's licensed

heat-treated factor VIII concentrate could have been distributed in Canada at any time in 1984, and Cutter's could have been distributed from mid-November of that year.

The bureau's licence for Hyland's heat-treated factor VIII concentrate had been granted at a time when HIV had not yet been discovered. As a result, Hyland had submitted no studies of HIV inactivation to the bureau nor made any claims about HIV inactivation. Although the bureau's licence for Cutter's dry heat-treated product was granted after the discovery of HIV, Cutter's licence application had not contained studies of HIV inactivation. However, Cutter's heat-treated factor VIII concentrate had been one of those used by Dr McDougal in his studies of the heat inactivation of HIV. Those studies had shown that Cutter's heat-treatment process effectively inactivated HIV. The heat-inactivation process used by Hyland was essentially the same. There were thus two acceptable heat-treated factor VIII concentrates licensed by the bureau at the time of its directives. This information is reflected in the file memorandum, previously quoted, written by Dr Davey on 9 November 1984 after a conversation with Dr Boucher, in which he said that "Hyland and Cutter heat-treated products are now licensed in Canada."

The Red Cross blood transfusion service could not immediately obtain heat-treated factor VIII concentrate custom fractionated from plasma it had collected. Its Canadian custom fractionator, Connaught Laboratories Limited (Connaught), did not have a heat-treatment process. Its U.S. custom fractionator, Cutter, had a process, but it could be used only if the concentrate had previously been stabilized through glycine precipitation in order to prevent a loss of activity in the factor VIII during heating, and none of the Red Cross plasma then in process had been so treated. It was estimated that the earliest that Cutter could supply the Red Cross with heat-treated custom-fractionated factor VIII concentrate was five to six months after processing began – that is to say, April 1985.

If one or more fractionators could be found that had stock in hand or in process, supplementary purchases might result in earlier deliveries of heat-treated factor VIII concentrate. Even so, it could take several weeks to issue a request for proposal (in effect, a call for tenders), receive and analyse bids made in response to the request, award a contract, finish processing (if no finished concentrate was in stock), and deliver the first shipment. The fastest way to obtain factor VIII concentrate was through spot purchase, provided a supplier had stock in hand or about to be finished. A spot purchase required only the issuing of a purchase order and delivery of the shipment, and any time needed to finish processing.

On 22 October 1984, the Red Cross issued a request for proposal for factor VIII concentrate, but it did not require that the concentrates be heat treated. The request was withdrawn nine days later, after a recommendation was made by the advisory subcommittee of the Canadian Blood Committee on 30 October, described in more detail below, that a consensus conference

be held to discuss whether conversion to heat-treated concentrates should occur. A new request, for heat-treated concentrates, was not issued until 14 December, after the consensus conference had been held and the Canadian Blood Committee had agreed to conversion. During November 1984, the Red Cross did not call for bids to supply heat-treated factor VIII concentrate and did not know how soon significant amounts could be obtained through supplementary or spot purchases.

On 26 November, Dr Davey informed Connaught that the Red Cross would send no more plasma for fractionation until Connaught had a licensed heat-treated factor VIII concentrate. Connaught would, however, be allowed to continue to deliver non-heat-treated concentrates already in process until the end of March 1985. On the same day, Cutter was instructed to use glycine precipitation and heat treatment in processing all factor VIII concentrate made from Red Cross plasma, and to heat treat all factor IX concentrate made from Red Cross plasma.

On 26 November, the Red Cross also began to make systematic inquiries into the availability of heat-treated factor VIII concentrate. The first step was to request information from fractionators in the United States and Canada. They were asked what capacity they had available for the custom fractionation of plasma supplied by the Red Cross and about the availability of commercial heat-treated factor VIII concentrate from other sources. This initial request for information was followed by telephone conversations and meetings.

None of the Canadian fractionators could yet produce heat-treated concentrates. Connaught, the only active fractionator, tentatively predicted that it would be licensed to distribute a heat-treated factor VIII concentrate in June 1985. The Winnipeg Rh Institute (Rh Institute), which had no licence to produce factor concentrates of any kind, was working to obtain one for heat-treated factor VIII concentrate by July. The Institut Armand-Frappier (Armand-Frappier) in Laval, Quebec, was hoping to begin construction of a fractionation plant in April 1985, with production to begin in mid-1986.

Internal memoranda of the Red Cross record its meetings with three U.S. fractionators. All three responded to the Red Cross question regarding custom fractionation. Cutter, on 4 December, expected that it could deliver the first heat-treated factor VIII concentrate custom fractionated from Red Cross plasma at the end of April 1985. Hyland, at a meeting the next day, foresaw little custom-fractionation capacity for 1985. Armour, the same day, said it would be willing to discuss custom-fractionation capacity if the Red Cross needed that service in 1985.

Although the Red Cross memorandum of the Hyland meeting records some discussion about the availability of commercial heat-treated factor VIII concentrate (that "no guarantee can be made that product can be available at short notice"), the Red Cross memoranda of the Cutter and Armour meetings are silent with respect to this issue. The question of the availability of commercial concentrates must have been discussed at all three meetings. Cutter and

Armour were represented by senior personnel, and they would not have failed to report on the availability of their commercial products. The memorandum prepared by the Armour staff about the meeting with the Red Cross on 5 December does indeed record a discussion of the availability of commercial concentrates; according to it, the Red Cross was interested in receiving commercial heat-treated factor VIII concentrate in April 1985, the month before it expected its supplies of non-heat-treated concentrates to run out, and had indicated that Armour could expect to supply it with 10 million units during 1985. Armour assured the Red Cross that it could begin deliveries by 1 April, so long as the Red Cross's order was placed by 1 February.

Because of the gaps in the documentary record, it is impossible to know precisely what the U.S. fractionators reported about the availability of their products at these meetings. In order to determine the quantity of heat-treated factor VIII concentrate that was available for purchase by the Red Cross in early December 1984, I requested information from the four U.S. fractionators. The requests were not particularly fruitful. The information was either not provided or was incomplete. Other evidence shows, however, that a significant quantity of heat-treated factor VIII concentrate was indeed available had the Red Cross ordered it by mid-December.

John Ryan, the president of Cutter, testified that in the late summer and autumn of 1984 Cutter had "a good working inventory" of heat-treated factor VIII concentrate that was finished and available for purchase. Inventory records for August and September 1984 show that Cutter had more than 40 million units on hand – equivalent to Canada's total annual consumption. Much of that amount had already been allocated to specific purchasers, but significant quantities were still available for purchase, especially by Cutter's regular customers. The Red Cross was not only a regular customer but, if not the biggest, one of Cutter's biggest customers. As such, it would have had preferential access to Cutter's unallocated inventory.

In October 1984, after the U.S. National Hemophilia Foundation recommended converting to heat-treated concentrates, demand for heat-treated factor VIII concentrate increased and Cutter's unallocated inventory decreased. Cutter was unable to provide inventory records for the crucial period October 1984 to January 1985, although it could do so for the periods immediately before and after that time. However, from other documents it appears that, at least until mid-December 1984, Cutter could have supplied the Red Cross with significant quantities of heat-treated factor VIII concentrate if it had been asked to do so. On 26 October 1984, Janis Peterson, Cutter's product manager, wrote to its sales representatives that there was "sufficient Koate-HT [Cutter's commercial heat-treated factor VIII concentrate] inventory to supply our customers and new customers immediately." Later, during December 1984, Ms Peterson told the U.S. National Hemophilia Foundation that, although use had increased since the foundation's recommendation of heat-treated concentrates, Cutter was not experiencing problems in

supplying heat-treated factor VIII concentrate. Furthermore, according to a Red Cross memorandum, Red Cross officials told officials of the Canadian Blood Committee, at a meeting on 29 November 1984, that "commercial purchases of heat-treated factor VIII can be made immediately from Hyland and Cutter Laboratories."

November 1984: Red Cross purchases of non-heat-treated commercial concentrates

The Red Cross continued to buy non-heat-treated factor VIII concentrate on the spot market after the Bureau of Biologics issued its directives. There are two versions of a Cutter note to file regarding a telephone conversation on 21 November 1984 between its sales representative and the Red Cross. Both versions say the Red Cross "wants an additional 2.8 Million [units of factor VIII concentrate] non HT [non-heat-treated]," set out some information about specific product lots, and report, "it has been decided to switch all Canada to HT." The sentence that follows differs in the two versions. In the original it reads, "Requirements to End-April can be GP [glycine precipitated], ultra-filtered or HT (HT not to be indicated *anywhere*)."

The three products mentioned were the three types of factor VIII concentrate available from Cutter: glycine-precipitated concentrates could be heat treated; ultra-filtered concentrates could not be heat treated; heat-treated concentrates were glycine-precipitated concentrates that had been heat treated. It is an irresistible inference that the reason for asking that the true nature of heat-treated concentrate not be indicated anywhere was to conceal the fact that heat-treated concentrates were available. In the second version of the note, the word "not" has been substituted in handwriting for "or" in the phrase "ultra-filtered or HT," and the words "(HT not to be indicated *anywhere*)" have been struck out. The sentence reads: "Requirements to End-April can be GP, ultra-filtered not HT." To ask Cutter not to supply heat-treated concentrates would ensure that they would be unavailable to users.

November 1984: The decision to create consensus on conversion

The issue of conversion to heat-treated factor VIII concentrate was first discussed by the advisory subcommittee of the Canadian Blood Committee at the same meeting, on 30 October 1984, that had recommended that the Red Cross create a three-month inventory of factor VIII concentrate. In a memorandum dated 29 October, Dr Naylor and Dr Derrick had suggested to Dr Perrault that a consensus conference be held to discuss conversion. When Dr Perrault put the suggestion before the advisory subcommittee, it was supported by Mr Poyser on behalf of the Canadian Hemophilia Society. Both Dr Martin Inwood, representing the Canadian Hematology Society, and Dr George Ross Langley, representing the Canadian Cancer Society, ultimately

supported the recommendation, but were concerned that calling a conference would result in delay and that the subcommittee should call for the conversion without any need for a conference. The recommendation was approved unanimously.

On 22 November, the executive committee of the Canadian Blood Committee, having reviewed the advisory committee's recommendation, agreed to sponsor a consensus conference, to be held on 10 December. Before 22 November, the Bureau of Biologics had issued its directive, and the purpose of the conference could no longer be whether the conversion should occur. During the executive committee's meeting, a telephone conversation was held with Dr Perrault. The minutes summarize Dr Perrault's position:

On the Canadian distribution and utilization of factor VIII, he suggested that the implementation should be phased carefully to avoid anxiety with hemophiliacs. On the Canadian fractionation industry, the impact is significant: if the CRC-BTS [Canadian Red Cross blood transfusion service] has to direct the plasma to Cutter U.S., Canadian self-sufficiency has to be seriously discussed. In fact, Canadian fractionators are very concerned about the issue.

Dr Perrault suggested that, though a decision is already taken by the Bureau of Biologics, there is an urgent need for a consensus conference to discuss the implementation of the decision and to minimize its impact on the consumers, the distributors, the fractionators and the CRC-BTS.

November 1984: The Red Cross implementation plan

On 19 November 1984, an assistant of Dr Naylor estimated that the Red Cross's inventory of non-heat-treated factor VIII concentrate would be exhausted during March or April 1985. Dr Naylor responded the next day in a memorandum headed "Timing of Distribution of Heat-Treated Factor VIII Concentrate":

1. As we discussed yesterday, heat-treated factor VIII concentrate should be introduced across the country at the same time.
2. The timing of its introduction depends on the amount of untreated factor VIII concentrate in inventory and in process.
3. Your memo of November 19th indicates that, if production at Connaught proceeds according to schedule, untreated concentrate can be phased out by approximately the end of April 1985.
4. As you point out, however, it is quite possible that production at Connaught will continue to be subject to sporadic lot failures.
5. In this eventuality, inventories of untreated factor VIII will be exhausted by the beginning of March 1985.
6. It should be possible to reissue the Request for Proposal for 1985 purchase of supplementary factor VIII, specifying all heat-treated, and to arrange for the initial deliveries to be on hand by the end of February 1985.

7. This arrangement should enable us to maintain flexibility to accommodate possible production problems at Connaught. However, should these occur, the most pragmatic approach will be the third scenario that you have described in your memo, viz. using any untreated plasma or factor VIII at Connaught for the production of a suitable, Canadian, heat-treated product, since distribution of unheated concentrate after the introduction of heated product will not be feasible.
8. No additional plasma should be shipped to Connaught until a suitable heat-treated factor VIII concentrate has been developed by this facility, otherwise the logistics of coordinated timing of the introduction of heat-treated concentrate will be further compromised.
9. We will have an opportunity to discuss these issues at this morning's meeting with Drs Davey and Derrick.

Dr Naylor's memorandum leads to the strong inference that the intention was to postpone the introduction of heat-treated factor VIII concentrate until the inventory of non-heat-treated concentrates had been exhausted. If heat-treated factor VIII concentrate was going to be introduced as soon as possible, as directed by the Bureau of Biologics, the "timing of introduction" would not have depended "on the amount of untreated factor VIII concentrate in inventory and in process," but on how quickly sufficient heat-treated concentrate could be obtained. Dr Naylor believed that heat-treated concentrates could be on hand by the end of February 1985. However, his outside date for phasing out non-heat-treated concentrates was the end of April 1985, a date related to the estimate of the time when non-heat-treated factor VIII concentrate would run out. Moreover, "the logistics of coordinated timing" must mean that the introduction of heat-treated concentrates was to be coordinated with the exhaustion of non-heat-treated concentrates.

The inference that there existed an intention to coordinate the introduction of heat-treated factor VIII concentrate with the exhaustion of non-heat-treated concentrates finds support in Dr Naylor's memorandum to file summarizing a telephone conversation he had on 4 December 1984 with Dr Robert Card, the chair of the medical and scientific advisory committee of the Canadian Hemophilia Society. In that conversation, Dr Card suggested that it might be possible to provide heat-treated concentrates to at least some hemophiliacs – those who had not previously used concentrates and were thus unlikely to have been exposed to HIV – as early as January 1985. In his response, Dr Naylor expressly referred to exhaustion of non-heat-treated concentrates; his memorandum says that he made Dr Card "aware of the more practical logistics, on the part of the CRCBTS [Canadian Red Cross blood transfusion service], of phasing in distribution of heat-treated coagulation factor products within a period of about four weeks to all users, coinciding with exhaustion of supplies of untreated products."

During November 1984, the Red Cross came to believe that the Bureau of Biologics would not impose a deadline for conversion. As a result of a conversation on 9 November between Dr Davey and Dr Boucher, the managers of the blood transfusion service believed they had reached an agreement with the bureau that four to six months was a reasonable period within which to achieve conversion. In that belief, and having an estimate that Connaught could deliver all its non-heat-treated factor VIII concentrate in process by the end of March 1985, Dr Davey wrote to Connaught on 26 November 1984 as follows:

In clarification of its direction, the BoB [Bureau of Biologics] has agreed that, up to March 1985, the CRCBTS [Canadian Red Cross blood transfusion service] can continue to accept factor VIII now in process which cannot be heat treated and to supplement Canadian supplies with unheated product to the extent that adequate supplies of heated concentrate cannot be secured. We are therefore prepared to receive AHF [antihemophilic factor] produced by your current process from FFP [fresh frozen plasma], already supplied, until March 31st, 1985, and hope that this will allow you time to process all such material.

A copy of this letter was sent to the bureau. Dr Furesz responded in a telephone call to Dr Naylor on 29 November, saying that he objected to the statement in the letter that the bureau had agreed to March 1985 as a deadline for the delivery of non-heat-treated concentrates. Dr Naylor's memorandum to file records Dr Furesz's additional comments:

[The] tabling [of] such a time frame as being in accordance with [the] BoB [Bureau of Biologics] direction implied that the Bureau was imposing rigid scheduling for introduction of heat-treated coagulation factor products. This is not the case since the policy of the BoB is to maintain, wherever possible, the utmost flexibility as to when new regulatory requirements should take effect and that this is based on the operational requirements of the organizations to which the regulations may apply ...

In the personal opinion of Dr Furesz, the CRCBTS [Canadian Red Cross blood transfusion service] should make its own decision as to the timing of the implementation of distribution of heat-treated coagulation factor products and this may have to include fractionation of all plasma by Cutter Laboratories until Canadian facilities can obtain appropriate licences.

10 December 1984: The consensus conference

As planned, the Canadian Blood Committee's consensus conference was held on 10 December 1984 in Ottawa. Although a "record of decisions" was later produced, comprehensive minutes were not kept, and there is no transcript

of what was said. However, position papers distributed by those who made presentations, notes kept by many persons recording both the presentations and the discussions that followed, and the testimony of several of the participants make it possible to describe most of what took place. The record of decisions characterizes the meeting as a "Consensus Conference on Heat-treated factor VIII" and describes its purpose as being "to discuss strategies for the implementation of the Bureau of Biologics decision."

The participants included representatives of the Canadian Blood Committee and its advisory subcommittee, the Red Cross blood transfusion service, the Bureau of Biologics and the Laboratory Centre for Disease Control of the federal Health Protection Branch, the National Advisory Committee on AIDS, the Canadian Hemophilia Society and its medical and scientific advisory committee, and the Canadian fractionators (Connaught, the Rh Institute, and Armand-Frappier). Although Dr Perrault had recommended to Dr Leclerc-Chevalier on 15 November that the U.S. fractionators be invited, the Canadian Blood Committee had not extended invitations to them. As a result of their absence, no one present could provide direct information about when and in what quantities those fractionators could supply heat-treated concentrates.

Dr Perrault, who acted as the chair, said in his introductory comments that, since the Bureau of Biologics had already decided that conversion to heat-treated concentrates should take place, the sole issue for discussion was when and how that conversion should occur. He added:

[I]t behooves this group gathered here to delineate and to pursue, with all cooperative vigour, a course by which the Bureau's decision can be implemented with the least delay, albeit with due consideration given wherever possible to the particular interests of those represented here today.

The particular interests represented were, in Dr Perrault's view:

- I. Users – primary, hemophiliacs; secondary, treaters
- II. Producers – primary, the Red Cross blood transfusion service; secondary, fractionators
- III. Funding group – primary, taxpayers; secondary, Canadian Blood Committee

The first presentations were by Dr Norbert Gilmore, the chair of the National Advisory Committee on AIDS, and Dr Alastair Clayton, the director general of the Laboratory Centre for Disease Control. They gave overviews of AIDS and its occurrence among hemophiliacs. Dr Furesz reviewed the reasons why the Bureau of Biologics had issued the directives on 16 November. He made the point, already understood by the Red Cross because he had conveyed it to Dr Naylor on 29 November, that the bureau was flexible with

respect to the timing of the conversion, and emphasized that the bureau had not imposed a deadline in its directive. The timing of the conversion was thus an open question.

Presentations by the blood transfusion service followed. Dr Davey reviewed the Red Cross's sources of supply and listed the implications of the bureau's decision that conversion take place. These implications were reduced yields of factor VIII concentrate; increased costs; increased processing time; and fractionation by U.S. companies only until a Canadian heat-treated concentrate was licensed. He reported that Red Cross plasma was now being sent to Cutter for processing into heat-treated concentrate.

Dr Naylor's address was the most important of the presentations made by the blood transfusion service with respect to the proposed timing of the conversion. He spoke from a written text, which includes the following passages:

With the rather complex logistics of ensuring continuity of supplies of essential blood products, it is not surprising that implementation of heat-treated coagulation factor products presents a particular challenge.

Because it is hoped that these products will offer a safer means of hemophilia therapy, hemophilia patients will want to use these as soon as possible in preference to untreated coagulation factor preparations. Consequently, the introduction of their distribution must be done in a fair and equitable way across the country, as soon as is feasible.

The fairest way in which this can be achieved is to coordinate the introduction of heat-treated factor VIII and factor IX concentrates at more or less the same time all across the country. Although this cannot be done overnight, we estimate that it will be possible to do this within a period of 8 weeks once all untreated products have been utilized and at the same time that the first deliveries are made of heat-treated concentrates.

The precise timing of implementing distribution of heat-treated factor VIII concentrates depends on several factors:

1. the current inventories of the untreated products at the National Office warehouse and at BTS [blood transfusion service] Centres, and the volumes of plasma that are already in process at fractionators and for which fractionation is already under way to produce untreated product;
2. the supplementary purchases which must be made each year, since we have to import about half of national requirements of factor VIII concentrates from commercial suppliers in the U.S.; these purchases will amount to at least 35 million units of factor VIII in 1985 and such purchases must be made since we do not collect sufficient plasma to produce this additional material;
3. return of the first batches of heat-treated factor VIII prepared from Canadian Red Cross plasma;

4. the time required for release testing of product by the BoB [Bureau of Biologics] which must be taken into account when scheduling delivery of purchased products or the return of products prepared from CRC [Canadian Red Cross] plasma;
5. the most effective method of heat treatment based on currently available evidence.

We can group all but the last of these factors together to project the time at which the distribution [of] heat-treated factor VIII can be implemented.

Thus, by considering current inventories of untreated product and that in process, the 1985 supplementary purchase, return of first batches of heat-treated product from CRC [Canadian Red Cross] plasma, and the BoB product release testing time, we believe that the implementation of distribution of heat-treated factor VIII concentrate should be possible at the beginning of May 1985 and could be completed across Canada within eight weeks after this date.

This projection can be made according to the rationale outlined on a hand-out which has been provided to you. If you refer to this, it can be seen that the estimated distribution for factor VIII concentrate in 1984 is 42,500,000 units and the average weekly distribution is projected at 817,300 units.

Current total inventories of untreated concentrate at BTS Centres, National warehouse, and in process at Cutter and Connaught amounts to 18,230,400 units. At average rates of distribution, this is just over 22 weeks supply, as of December 1st, 1984, and thus these will be exhausted by about May 1st, 1985. By this time, the CRC BTS should also have received the first shipments of heat-treated factor VIII concentrate prepared from CRC plasma and the first deliveries of the supplementary commercial purchase of similar product.

To ensure a complete conversion to heat-treated factor VIII within a period of 8 weeks following the May 1st introduction date, it may be necessary to move inventories of unheated product from regions where there may be excess to others in short supply, to ensure that supplies of untreated product are exhausted across the country at more or less the same time.

Dr Naylor's statement that the supply of non-heat-treated factor VIII concentrate would be exhausted by about 1 May cannot be reconciled with his statement that the conversion to heat-treated concentrate would be completed eight weeks thereafter. If the non-heat-treated concentrate had been exhausted by 1 May, there could not have been an eight-week period thereafter in which both non-heat-treated and heat-treated concentrates were to be distributed. Of necessity, the conversion to heat-treated concentrate would have to have been completed by about 1 May because there would have been nothing but heat-treated concentrate to distribute thereafter.

The Red Cross, through Dr Naylor's presentation, proposed a plan under which the inventory of non-heat-treated factor VIII concentrate would be exhausted during the conversion process, no matter when supplies of heat-treated concentrate were obtained. The words "once all untreated products have been utilized" and "to ensure that supplies of untreated product are exhausted across the country at more or less the same time" admit of no other meaning. Moreover, unless there was an intention to exhaust the inventory, "the current inventories of the untreated products ... and the volumes of plasma that are already in process" would not have been factors in the timing of the conversion; the only relevant question would have been how quickly heat-treated products could be obtained. Dr Naylor's presentation made no mention of the means by which heat-treated concentrates could be introduced as soon as possible. Rather, there was a simple statement that the first deliveries of heat-treated concentrate should be received by 1 May 1985.

Another representative of the Red Cross then reviewed for the consensus conference "the substantial economic impact because of yield losses and additional processing costs" that would occur with conversion. His review was consistent with a plan that all non-heat-treated concentrate be used in the process of conversion. One of the variables that would influence the "final implementation date," he said, was the delivery of non-heat-treated factor VIII concentrate still being processed at Connaught. Concern about this variable is inconsistent with a determination to bring about full conversion as soon as possible.

Dr Card, as the chair of the Canadian Hemophilia Society's medical and scientific advisory committee, represented the society at the conference and gave the next presentation. He urged that heat-treated concentrates be introduced as soon as possible. There were differing recollections, however, whether he also endorsed the Red Cross's proposal that the inventory of non-heat-treated factor VIII concentrate be exhausted in the conversion process. Dr Card proposed an implementation strategy that, according to his speaking notes, would see heat-treated factor "introduced as available," initially for the essential treatment of newly diagnosed and mild hemophiliacs, without any geographic preference, and "in essence [saw] the severe multiply-treated hemophiliacs using up the stocks of non-heat-treated product." Dr Card's proposal was based on his view of the level of risk to severe hemophiliacs if they continued to use non-heat-treated concentrates. As he said at the conference, he believed that any severe hemophiliac who had received many units of non-heat-treated concentrate had probably already been exposed to HIV, and had likely either developed an immunity to it or was on his way to developing AIDS. For those on their way to developing AIDS, he said, "[n]othing we will do today will change that." It is unclear why Dr Card made this proposal. What is clear is that, either because of his belief regarding risk or because of his reliance on information from Dr Naylor, he, unlike other physicians and a lay representative of the Canadian Hemophilia

Society later in the conference, did not oppose the Red Cross proposal to exhaust the inventory of non-heat-treated factor VIII concentrate. Indeed, he left other participants with the impression that he supported it.

The last presentations were given by representatives of Connaught, the Rh Institute, and Armand-Frappier. All three briefly described their current capabilities and estimated when they would be licensed to distribute heat-treated factor VIII concentrate. Connaught and the Rh Institute said that they expected to receive licences for heat-treated factor VIII concentrate by 1 July 1985. Armand-Frappier said that its proposed fractionation plant would not be ready for production until April 1986 at the earliest.

A period of discussion followed the presentations. Dr Inwood, Dr Peter Koopmann, and Dr T.F. McElligott, all senior physicians, all members of the advisory subcommittee of the Canadian Blood Committee, and each attending the conference as a representative of an important medical institution – respectively, the Canadian Hematology Society, the Canadian Medical Association, and the Canadian Association of Pathologists – began the discussion. All emphasized the need to obtain heat-treated concentrates at the earliest possible opportunity and condemned any suggestion that the inventory of non-heat-treated factor VIII concentrate had to be exhausted before heat-treated concentrates were introduced. Dr Koopmann called for the introduction of heat-treated concentrates as soon as possible, even if this meant the destruction of the inventory of non-heat-treated concentrates; he said heat-treated concentrates should be bought on the spot market if that was necessary to introduce them as soon as possible. Dr Inwood advocated the introduction of heat-treated concentrates with the shortest possible transitional period, if one was necessary, and recommended that physicians treating hemophiliacs be given the task of developing criteria for the use of heat-treated concentrates during the transition. Dr McElligott expressly rejected exhausting the inventory of non-heat-treated concentrates and called for conversion to heat-treated concentrates as soon as possible.

In their testimony, Dr Inwood and Dr Koopmann said they had understood Dr Naylor's presentation to be a proposal to exhaust the Red Cross inventory of non-heat-treated factor VIII concentrate during the conversion process. Dr Inwood testified that Dr Naylor was "unwilling to have heat-treated concentrate immediately available to the hemophilia population in Canada." He added:

To do justice to the late Dr Naylor, I suspect that he wanted to get across to us his opinion that they would not be able to get any heat-treated material until April, and as a result, we would have to continue using non-heat-treated material. But I can assure you that at the consensus conference, and it was a matter of some significant debate during the lunch time, that they certainly wanted to finish off their stocks at the same time.

Dr Inwood also said, "there is no doubt, the intent was that we would have to finish up the existing stocks." Dr Koopmann testified that Dr Naylor's presentation included the "idea of using up stock." He recalled Dr Inwood, Dr McElligott, Dr Card, Dr Langley, and Dr Georges-Étienne Rivard (a physician who treated hemophiliacs and who attended the consensus conference as a member of the Red Cross's volunteer national blood transfusion service advisory committee) discussing the issue of exhausting the old stock "very hotly."

That Dr Naylor's presentation included a planned exhaustion of the inventory, and that there was a vigorous response to that plan, is confirmed in a contemporaneous Connaught memorandum. It described that presentation as follows:

Existing inventory of non-heated AHF [antihemophilic factor] is estimated to last 22.3 weeks. On this basis the objective is to introduce heat-treated AHF by May 1st, 1985 by which time inventories of non-heat-treated product would be depleted.

This statement generated wide-range discussion on the legal and ethical implications arising if heat-treated product became available prior to May 1st, 1985: should introduction of heat-treatment be delayed until all non-heat-treated inventories are depleted or should the CRC [Canadian Red Cross] be prepared to discard non-heat-treated inventories. This question was unresolved.

Dr Inwood testified that this description was "absolutely correct."

In their testimony, Dr Perrault and Dr Davey denied that Dr Naylor had proposed to the conference that the inventory of non-heat-treated factor VIII concentrate be exhausted during the conversion process. The same denial is implicit in the submissions made to me by the Red Cross. In essence, both in the testimony and the submissions, the position taken is that the Red Cross conducted bona fide surveys of the time when non-heat-treated factor concentrates would run out (be "exhausted") and when heat-treated concentrates would become available, and that it was coincidence that the surveys showed that these two events would occur at about the same time – the end of April or beginning of May 1985. The contemporaneous documentation of the meeting and the testimony of Dr Inwood and Dr Koopmann, which I accept, contradicts the position of the Red Cross.

Eleven recommendations were drafted near the end of the conference. It was upon reading those recommendations that Mr Poyser, a lay representative of the Canadian Hemophilia Society, spoke for the first time. He testified that he had become increasingly frustrated as he listened to the presentations and discussion because the participants had been talking about using the non-heat-treated concentrates and the costs of conversion instead of focusing on

ways to introduce heat-treated concentrates as soon as possible. He felt he was being asked to choose between recommendations that were all unacceptable. He therefore put forward his own recommendation, that "the conference has come to a consensus that as a policy we support the immediate and exclusive use of heat-treated factor VIII and IX."

In the end, no clear consensus was reached by the conference on the timing of the conversion from non-heat-treated to heat-treated concentrates. A consensus was reached, however, on one aspect of the conversion – that the medical and scientific advisory committee of the Canadian Hemophilia Society would develop guidelines, which came to be called "the protocol," for the allocation of heat-treated concentrates if and while the available quantities of them were insufficient to treat all hemophiliacs. The time when the new concentrates might be available in only limited quantities came to be called the "transitional period." Three other major issues arising from the conference remain open to differing interpretation.

First, it is unclear exactly what final recommendations were approved. Eleven recommendations were drafted during the conference, but only nine were presented to the executive committee of the Canadian Blood Committee the next day. Which version was approved at the conference is important, for there is a significant difference in the wording of the principal recommendation. Some participants believed that the eleven recommendations had been approved. Dr Koopmann and Dr Langley left the conference with this impression, and the Connaught representative's memorandum of the conference also mentions eleven recommendations. However, the federal government produced in evidence an eleven-recommendation version that had been edited by hand down to nine recommendations. Dr Leclerc-Chevalier could remember only the nine-recommendation version, and the record of decisions supports her recollection. It records:

Participants to the Conference, with the exception of the Chairman, Dr Perrault, and CBC [Canadian Blood Committee] members, discussed all aspects of the issue and, under the guidance of Dr Norbert Gilmore, developed a series of recommendations. The full Conference reconvened to discuss the recommendations.

A consensus was reached on nine recommendations to the Canadian Blood Committee.

Dr Inwood recollected that there was no formal approval of either version at the conference. In his testimony, he described the recommendations as "a concoction of all of the various recommendations made by individuals." Which version was approved by the conference cannot be determined because of the contradictory nature of the evidence.

Second, the conference's recommendation about the timing of the transition to heat-treated factor VIII concentrate remains a subject of controversy. The primary recommendation in the two versions carried potentially different meanings as a result of an added word, emphasized below, in the second.

Eleven-recommendation version

That this Conference endorses the introduction of heat-treated factor VIII concentrates in Canada as soon as is feasible before May 1985, with a transition period not exceeding eight weeks when both heat- and non-heat-treated will be transfused to Canadian hemophiliacs.

Nine-recommendation version

That this Conference endorses the introduction of heat-treated factor VIII concentrates in Canada as soon as is feasible before May 1985, with a transition period not exceeding eight weeks *thereafter* when both heat- and non-heat-treated will be transfused to Canadian hemophiliacs. [Emphasis added.]

Dr Koopmann and Dr Langley understood that the transition was to end by 1 May 1985. Dr Inwood understood the recommendation was for transition as soon as supplies could be obtained, with purchases to be made wherever possible; he also understood that the transition was to end by 1 May 1985. Dr Card, however, believed that the transition was to begin 1 May 1985; as a consequence, he did not put the development of the protocol defining priorities for access to heat-treated concentrates during the transitional period before the medical and scientific advisory committee of the Canadian Hemophilia Society until 19 April 1985. There was thus a serious divergence of understanding among the physicians attending the conference. Other views on this subject are discussed below.

Third, no clear decision was made whether the introduction of heat-treated factor concentrates should be delayed until the inventory of non-heat-treated factor VIII concentrate was exhausted, as proposed by the Red Cross through Dr Naylor. Dr Koopmann, Dr Langley, and Dr Inwood understood that heat-treated concentrates were to be distributed to all hemophiliacs as soon as sufficient quantities were available. The Connaught memorandum of the meeting records that the issue was "unresolved." Other views on this subject are also discussed below.

11 December 1984: The Canadian Blood Committee's adoption of the consensus conference recommendations

The executive committee of the Canadian Blood Committee held an extraordinary meeting on 11 December 1984 to consider the recommendations of the consensus conference. According to the minutes of the meeting, it

considered nine recommendations, on which it understood consensus had been reached. They read:

1. That this Conference endorses the introduction of heat-treated Factor VIII concentrates in Canada as soon as is feasible before May 1985, with a transition period not exceeding eight weeks thereafter when both heat and non-heat-treated will be transfused to Canadian hemophiliacs.
2. That this Conference ask the Canadian Bureau of Biologics to expedite licensing of further heat-treated Factor VIII in Canada, including approval of heat-treatment procedures for material in process in Canada.
3. That this Conference recommends that all Factor VIII products currently in the plasma or cryoprecipitate stages should be heat-treated.
4. That this Conference recognizes that the CRC [Canadian Red Cross] will continue to direct all FFP [fresh frozen plasma] to facilities currently licensed to produce heat-treated Factor VIII until Canadian fractionators are licensed to produce heat-treated concentrates, when the CRC will redirect plasma to licensed Canadian facilities.
5. That this Conference recommends that the CBC [Canadian Blood Committee] recognize costs of development of heat-treated Factor VIII concentrates as legitimate costs to be met through sales of fractions by the CRC to the provinces.
6. That this Conference recommends the CBC continue surveillance of and promote and support further research by primary and secondary producers towards the development of safer Factor VIII concentrates.
7. That this Conference recognizes that it is most important that the CBC continue to support the development of self-sufficiency in fractionation products in Canada.
8. That this Conference recommends that the criteria for the use of heat-treated and non-heat-treated concentrate during the transition period be agreed upon by the hemophilia treaters who are members of the Medical/Scientific Advisory Committee of the CHS [Canadian Hemophilia Society], using existing national representation.
9. That this Conference recommends that the CBC encourage national efforts to continue surveillance, serological investigations and other research in an effort to understand the effects of retrovirus infections on hemophiliacs.

The executive committee reviewed and adopted those recommendations and gave the Red Cross the "responsibility for implementing" numbers 1, 3, 4, and 8.

During the meeting some members of the executive committee expressed uncertainty about the timing of the transition to heat-treated factor VIII concentrate. According to the minutes:

It was obvious that the Conference had endorsed a decision of the Bureau of Biologics, Health Protection Branch, but there were some uncertainties regarding the timing for the eight-week transition period. It was decided to ask for clarification from Dr Perrault, who had accepted to meet with the Executive Committee at their convenience.

In other words, it was not only the physicians at the consensus conference who were divided as to when the transition to heat-treated factor VIII concentrate was to take place. The members of the executive committee, most of whom had attended the conference the day before, were also unclear about what had been decided.

Dr Perrault joined the meeting later. According to the minutes, he said that

the Conference endorsed a “fait accompli” and addressed the “as soon as possible” mentioned in the Bureau of Biologics’ decision, choosing May 1, 1985 as the most reasonable time frame for implementing the decision, with a transition period of eight weeks which could start any time from now but, [at] the latest, on May 1, 1985.

Dr Perrault’s position, that the transition could begin at any time but no later than 1 May 1985, became the operative one.

Dr Perrault apparently believed, as did the author of the Connaught memorandum describing the conference, that no decision had been reached on the subject of exhausting the inventory of non-heat-treated factor VIII concentrate during the conversion process; it was thus an open question whether the inventory of non-heat-treated concentrate was to be exhausted before distribution of the heat-treated concentrate to all hemophiliacs could begin. The relevant portion of the executive committee meeting minutes reads:

Dr Perrault added that, as far as he is concerned, the inventory has to be dealt with, unless the CBC [Canadian Blood Committee] tells him to write it off, which was not requested by the Conference and more specifically by the Canadian Hemophilia Society.

The following testimony about that passage from the minutes was given by Ambrose Hearn, the chair of the Canadian Blood Committee at the time:

I would interpret this note to say this. We have just had a consensus conference. We have dealt extensively with this issue. We have a series of recommendations coming from this consensus conference. The issue of inventory

has not been the subject of a recommendation from the consensus conference. It is now coming to the Canadian Blood Committee, all of the recommendations to be dealt with by the Canadian Blood Committee.

Dr Perrault would say to the Canadian Blood Committee, "It would be my intent to use up the inventory, because frankly, I have no recommendation to the contrary, coming out [of] the scientific advisory committee [of the Canadian Hemophilia Society]. Furthermore, I am going to my own internal scientific advisory committee to deal with how it will be dealt with. I have nothing coming from the Canadian Hemophilia Society."

We would have simply accepted that as the statement of intent to proceed.

The minutes, which show no response to Dr Perrault's statement, together with this testimony, demonstrate that the members of the Canadian Blood Committee who attended the conference thought that the disposition of the non-heat-treated inventory had not been decided there; that Dr Perrault had therefore put the issue before the executive committee for a decision; that the committee was silent about whether leftover inventory would be written off; and that it left that inventory, in the words of the minutes, "to be dealt with" by Dr Perrault. Mr Hearn's testimony, set out above, was given late in the day on 9 August 1995.

On the morning of 10 August 1995, before commission counsel resumed her questioning, Mr Hearn made an opening statement in which he said that Dr Perrault *did not* put the inventory issue before the executive committee for a decision, since that issue *had* been resolved at the conference. He said:

If I could, I want to see if I can clear up a little confusion that I may have had yesterday afternoon. And the confusion that I had seemed to say that, or seemed to signal that the committee had some information or that the Red Cross had made a proposal to the committee by virtue of a kind of a mid-sentence pause from Dr Perrault about inventory, and that we had not responded to that.

I think, first, I need to say to you that – for context – in my experience in all of the time dealing with the Red Cross, it was actually never shy about presenting an issue to the CBC [Canadian Blood Committee]. It did it either verbally, or it did [it] in writing, or it did it in a multitude of ways, and usually was quite – the Red Cross was quite clear what it wanted from the CBC. It didn't do it by way of nuance or innuendo, or in any way in that sense.

And if I might bring you back to the whole episode itself, if we think of the consensus conference and you went through all of the debate yesterday there, and there were various references and so on. And it is clear that all of the senior officials from the Red Cross were at the consensus conference. It is clear that all of the members of the advisory committee

to the CBC were at the consensus conference, and others. And some of the CBC members were there. And some remember being there and some don't.

But it is clear the discussion occurred around the issue of the inventory, how it was going to be done. I think that is clear in the consensus conference. I would submit to you that actually the recommendations coming out of the conference deal with that issue.

Mr Hearn went on to say that there had been no need for the executive committee to make a decision since it had been expected that, in light of the Red Cross's presentation at the conference, the inventory of non-heat-treated factor VIII concentrate would already have been exhausted by the time sufficient heat-treated concentrate arrived.

There was no confusion in Mr Hearn's testimony on 9 August 1995. The minutes of the executive committee meeting show that Dr Perrault put the inventory question before the committee for decision ("the inventory has to be dealt with, unless the CBC tells him to write it off").

20 December 1984: The announcement of the consensus conference recommendations

The Canadian Blood Committee's executive committee agreed on 11 December with a suggestion by Dr Perrault that the consensus conference recommendations be publicized in a press release to be issued jointly by the Red Cross and the Canadian Hemophilia Society. On 17 December, Dr Derrick and Dr Naylor, on behalf of the Red Cross, drafted a release, which began with the following statement:

During the last four months heat-treatment procedures which effectively inactivate viral agents that can cause serious disease, among them the retroviruses believed to cause AIDS, have been introduced by some manufacturers into the preparation of factor VIII concentrate and factor IX complex coagulation factors used to treat hemophiliacs.

Accordingly, on November 16, 1984 the Bureau of Biologics, Health and Welfare Canada, issued a directive recommending that non-heat-treated coagulation factor products be replaced in Canada as soon as possible by those which have been heat-treated.

The draft release was sent to Dr Card of the Canadian Hemophilia Society and Dr Leclerc-Chevalier of the Canadian Blood Committee for comment. On 18 December, Dr Leclerc-Chevalier discussed it with Dr Furesz of the Bureau of Biologics, who suggested an alternative opening:

There is some evidence to suggest that infection with HTLV-III virus [HIV], commonly believed to be the causative agent of acquired immunodeficiency syndrome (AIDS), *is associated* with the use of coagulation factor

products. These products are life saving in the treatment of patients with hemophilia. During the last four months heat-treatment procedures, used by some manufacturers in the preparation of coagulation factor products, have been shown to effectively inactivate HTLV-III virus.

Accordingly on November 16, 1984 the Bureau of Biologics, Health and Welfare Canada, issued a directive to all manufacturers of coagulation factor products recommending that presently used products be replaced in Canada as soon as feasible by those which have been heat-treated. [Emphasis added.]

On 20 December, Dr Davey telephoned Dr Leclerc-Chevalier to say that Red Cross lawyers objected to the emphasized words in Dr Furesz's suggested opening. The Red Cross lawyers wanted the sentence in which those words appeared to read:

It has been suggested that infection with HTLV-III virus [HIV], commonly believed to be the causative agent of acquired immunodeficiency syndrome (AIDS), may be associated with the use of coagulation factor products. [Emphasis added.]

The wording proposed by the Red Cross's lawyers reflects a concern about questions of liability. The Red Cross, on the advice of its lawyers, did not want a statement made from which it could be inferred that the Red Cross was admitting that non-heat-treated concentrates, which the Red Cross would continue to distribute for some time, carried a high risk of HIV infectiveness. Dr Leclerc-Chevalier, however, thought that the emphasized words in the Red Cross version were so vague that they no longer supported the bureau's action. The wording eventually used in the press release on 20 December appears to have been a compromise between that proposed by Dr Furesz and that of the Red Cross:

There is some evidence to suggest [Dr Furesz's words] that infection with HTLV- III virus, commonly believed to be the causative agent of acquired immunodeficiency syndrome (AIDS), may be associated [the Red Cross lawyers' words] with the use of coagulation factor products. [Emphasis added.]

The language used in the release significantly qualified the risk from non-heat-treated concentrates. A reader would have reasonably inferred that conversion to heat-treated concentrates was far from urgent. Indeed, the wording in the press release was even weaker than that found in the article written by Dr Naylor and Dr Derrick two months earlier, in which they said that there was some evidence to suggest that HIV infection "is" associated with the use of concentrates. Eight days after the press release, Dr Derrick and Dr Davey linked the use of non-heat-treated factor concentrates and

the risk of infection with AIDS much more clearly. In the statement drafted for publication in the *Canada Diseases Weekly Report*, a publication of the Laboratory Centre for Disease Control, they wrote: "The use of coagulation factor concentrates is thought to be the primary, although not necessarily the only, causative factor in the development of AIDS in [hemophiliacs]."

The press release, after describing the participants at the conference, concluded as follows:

The consensus reached by this group was that the introduction of heat-treated coagulation factor preparations in Canada could be accomplished before May 1985 with a period of transition from the use of non-heat-treated to the use of heat-treated products not to exceed eight weeks thereafter.

The conference further agreed that the criteria for the use of heat-treated and non-heat-treated products during this transition period would be determined by the hemophilia treaters who are members of the Medical and Scientific Advisory Committee of the Canadian Hemophilia Society.

Thus, according to the release, conversion was to begin at a yet unknown date before May 1985, with the provision of heat-treated concentrates to hemophiliacs who met the criteria to be determined by the medical and scientific advisory committee of the Canadian Hemophilia Society. It was to end no later than eight weeks after that unknown date, with the distribution of heat-treated concentrates to all hemophiliacs. In the statement that they drafted for inclusion in a publication by the National Advisory Committee on AIDS in the *Canada Diseases Weekly Report*, Dr Davey and Dr Derrick wrote that "by May 1985 all factor VIII concentrates and factor IX complex provided for treatment of hemophilia in Canada will be heat-treated for inactivation of retroviruses."

January 1985: The award of contracts for heat-treated factor VIII concentrate

On 11 December 1984, Dr Naylor instructed an assistant to issue a request for proposal for the supply of heat-treated factor VIII concentrate. He also asked him to analyse what had to be done to meet the commitment the blood transfusion service had made at the consensus conference the previous day. By this time, seventy-three days had passed since the publication of the Levy article reporting that heat treatment inactivated some retroviruses, forty-six days since the Centers for Disease Control had reported that heat treatment inactivated HIV, forty-three days since Dr Naylor and Dr Derrick had reported the value of heat treatment to Dr Perrault, and twenty-five days since the Bureau of Biologics had directed the conversion to heat-treated concentrates.

The analysis requested by Dr Naylor was contained in a memorandum dated 11 December, which began:

As per our conversations and based on the commitments made in Ottawa on 10 Dec 84 viz, that heat-treated AHF [antihemophilic factor] would be available and in general distribution not later than May 1985 and that the CRC BTS [Canadian Red Cross blood transfusion service] would withdraw all non-heat-treated material on July 1, 1985, it is imperative that the RFP [request for proposal] for AHF concentrate be issued this week.

The memorandum went on to list unknown factors and "known facts" affecting the estimates of supply and demand for factor VIII concentrate. One of these known facts was that "a three month inventory has been accepted by the CBC [Canadian Blood Committee] as the minimum operating requirement."

Two weeks earlier, on 26 November, the Red Cross had asked Cutter to heat treat all factor VIII concentrate still to be manufactured from plasma supplied by the Red Cross. It knew, however, that those concentrates would not begin to arrive until April 1985 at the earliest. In mid-December it took two additional steps to obtain heat-treated factor VIII concentrate for delivery in the first half of 1985. On 14 December, it issued a request for proposal for supplementary contracts for heat-treated concentrates to be delivered between April 1985 and March 1986. Five days later, it ordered four million units of heat-treated factor VIII concentrate from Cutter, its first spot purchase of this kind of concentrate. That concentrate was already in process, but the first lots would not be delivered to the Bureau of Biologics for review of quality and regulatory release until February 1985, or to the Red Cross for distribution until the end of April 1985.

On 31 January 1985, the Red Cross, after analysing the responses to its request for proposal, decided to award contracts for supplementary purchases of heat-treated factor VIII concentrate to Cutter (thirty million units) and Armour (ten million units). The contract awarded to Armour was conditional on its receipt of a licence from the Bureau of Biologics for its heat-treated factor VIII concentrate. Dr Davey explained, in a letter dated 18 February to Dr Leclerc-Chevalier, why the Red Cross had decided to use two suppliers, despite an additional cost of U.S.\$370,000. He first explained how an estimated requirement of forty million units had been calculated and said that all concentrates offered were technically acceptable. He then said that two of the four bids, those from Alpha and Hyland, had been rejected because of price; that Cutter had submitted the lowest bid; but that it had seemed imprudent to obtain the entire amount from one fractionator while there was a general shortage of supply. The situation had changed since November and early December 1984, when supplies of heat-treated concentrate were more readily available, because of increasing demand for those products. Dr Davey told Dr Leclerc-Chevalier that "conversations with various U.S. contacts had indicated that

there is no ready availability of heat-treated factor VIII for spot purchases and even long-term purchases under contract cannot be absolutely guaranteed delivery on schedule by the supplier."

On 11 March, Cutter reported that it was unable to meet the delivery schedule under its supplementary contract and that the first delivery of heat-treated factor VIII concentrate under the contract might not arrive until the end of June 1985. The explanations given by Cutter were overselling of production and poor inventory management.

March–April 1985: Preparations for conversion

On 20 March 1985, Dr Naylor sent the medical directors of the seventeen Red Cross blood centres the first of four memoranda about the distribution of heat-treated concentrates. It began:

On November 16th, 1984, the Bureau of Biologics, Health and Welfare, Canada, issued a directive to all manufacturers and distributors of coagulation factor products recommending that such products be replaced in Canada as soon as feasible by those which have been heat-treated.

As a result, a consensus development conference was called by the Executive Committee of the Canadian Blood Committee to determine how and when these recommendations might best be implemented.

The consensus reached at the conference was that the introduction of heat-treated coagulation factor products in Canada could be accomplished by May 1st, 1985, with a period of transition from the use of non-heat-treated to the use of heat-treated products not exceeding eight weeks thereafter.

Despite the references to the bureau's directive that conversion take place "as soon as feasible" and to a decision at the conference that the introduction of heat-treated concentrates "could be accomplished by" 1 May, with a transitional period "not exceeding eight weeks thereafter," the memorandum goes on to describe a fixed schedule, 1 May to 1 July, for the transitional period:

During the period May 1st to July 1st, 1985, limited amounts of heat-treated factor VIII concentrate and factor IX complex will be distributed to BTS [blood transfusion service] Centres. The greater proportion of coagulation factor products will continue to be supplied in non-heated form during this transition period.

After July 1st heat-treated coagulation factor products will be made exclusively available and non-heat-treated products will no longer be distributed.

During the transition period May 1st–July 1st, all Centres will receive small amounts of heat-treated factor VIII and factor IX that will be a proportion of their normal monthly utilization; this proportion will be determined according to the estimated number of patients that are eligible to

receive heat-treated products preferentially according to the criteria that will be established at the April 19th meeting of the CHS MSAC [Canadian Hemophilia Society medical and scientific advisory committee]. The majority of hemophilia patients that have been on long-term concentrate therapy will continue to be supplied with non-heat-treated products until after July 1st.

On 12 April the Bureau of Biologics issued a licence for Armour's heat-treated factor VIII concentrate. Cutter's had been licensed in November 1984. The Canadian labelling for the products had not yet been prepared and approved, however. On 25 March 1985, when the Red Cross needed the rapid release of 12,000 vials of Cutter's heat-treated factor VIII concentrate, the bureau allowed the vials to be distributed with U.S. labelling augmented by stickers containing information required by the bureau. Similarly, on 12 April 1985, when the bureau issued a licence for Armour's heat-treated factor VIII concentrate, it allowed Armour to use U.S. labelling with a sticker. All heat-treated factor VIII concentrate ordered by the Red Cross could now be distributed in Canada as soon as it was received.

On 15 April, the advisory subcommittee of the Canadian Blood Committee met for the first time since the consensus conference. At that meeting, Dr Perrault described the supplementary purchases. Mr Poyser, still the representative of the Canadian Hemophilia Society on the subcommittee, asked why, given a purchase of forty million units of heat-treated factor VIII concentrate, the conversion to the heat-treated products had not already been completed. Dr Perrault explained that the forty million units would be received over a twelve-month period. He then described the transitional period. The relevant portion of the minutes states:

Dr Perrault answered that it was a decision of the consensus conference that there would be a two-month transition period.

In a letter to Dr Leclerc-Chevalier, Dr Perrault asked that this statement in the minutes be amended to read:

Dr Perrault answered that it was a decision of the Consensus Conference that there would be a two-month transition period, during which a mixture of both non-heat-treated (still in inventory) material would be distributed along with the first available heat-treated material.

In both versions, Dr Perrault attributed to the consensus conference a decision that there "would be a two-month transition period," a view consistent with the fixed schedule set out in Dr Naylor's memorandum to the medical directors. In fact, the consensus conference had recommended that the

introduction of heat-treated concentrates should occur "as soon as is feasible before May 1985" and that the transitional period should not exceed eight weeks.

In April 1985, the Red Cross received information about a problem that could have affected the timing of the conversion. At that time, the Red Cross learned that every lot of heat-treated factor VIII concentrate in process at Cutter "apparently contained suspect plasma" and that one lot contained plasma "implicated" in cases of transfusion-associated hepatitis B. This meant that, in the one lot, at least one unit of plasma that had been used as raw material had come from a person who *might* have had hepatitis B and that the other lots might also contain plasma implicated in hepatitis transmission. Unless the Bureau of Biologics approved the distribution of these lots, the only heat-treated factor VIII concentrate that would be available in Canada would be the ten million units ordered from Armour, and they would fall far short of the national need. On 25 April, the Red Cross blood transfusion service asked the Bureau of Biologics to decide whether lots of heat-treated factor VIII concentrate containing plasma implicated in hepatitis B transmission could be distributed. On 13 May, the Bureau of Biologics told the Red Cross that the lot known to contain implicated plasma could be distributed, and gave several reasons for its decision. To destroy the lot would delay the conversion to heat-treated concentrates and might lead to a serious shortage of concentrates for the routine treatment of hemophiliacs. Furthermore, given the large size of the plasma pool, the concentration of virus would have been diluted to a level at which it was no longer dangerous, the hepatitis B antibody that was also present in the plasma pool would likely have inactivated any virus that was present, and any virus that survived the antibody would probably have been inactivated by the heat treatment.

April 1985: Guidelines for the allocation of heat-treated concentrates

At the consensus conference, it had been agreed that guidelines were needed for the allocation of heat-treated concentrates and that they would be created by the medical and scientific advisory committee of the Canadian Hemophilia Society. These guidelines, or "the protocol," as they collectively came to be called, were to be in effect for a transitional period of at most eight weeks, if there was in fact a period during which supplies of heat-treated concentrates were insufficient to meet demand.

In order to understand how the medical and scientific advisory committee intended the criteria in the protocol to be used, it is necessary to review the positions of the same advisory committee with regard to the distribution of factor concentrates on two earlier occasions. The first occurred in 1978, when the Red Cross began to distribute factor VIII concentrate. The advisory committee decided then that, during the transition from cryoprecipitate,

each hemophilia treatment clinic should develop its own guidelines on which of its patients should be treated with concentrates until there was enough to treat them all. The Red Cross's role during the transitional period was to be limited to distribution of the concentrates throughout the country. The Red Cross endorsed this position and notified the medical directors of the seventeen blood centres accordingly.

The second occasion was in 1982, when the advisory committee developed a comprehensive set of categories for treatment with a product known as Autoplex – one of various specialized products developed to help hemophiliacs whose bleeding could not be controlled by standard factor concentrates. Autoplex was both expensive and dangerous if used improperly, and was stocked in limited quantities. In essence, the guidelines established by the advisory committee restricted access to hemophiliacs for whom treatment with standard factor concentrates was ineffective. The process for determining whether a hemophiliac should be treated with Autoplex was set out as follows: "The RCBTS [Red Cross blood transfusion service] director and the provincial MSAC [medical and scientific advisory committee] chairperson will appoint a resource person (consultant) with whom cases will be discussed and who will verify the indications for the release and use of Autoplex." The Red Cross medical directors were thus given an indirect role in determining whether Autoplex should be released for the treatment of hemophiliacs.

On 23 March 1985, a meeting was held of the medical and scientific advisory council of the Ontario chapter of the Canadian Hemophilia Society (not to be confused with the national organization's medical and scientific advisory committee). Dr Naylor attended the meeting and described the supplementary contracts for forty million units of heat-treated factor VIII concentrate. He told the council that the deliveries from the manufacturers "would commence in May and there would be an increasing percentage of heat-treated product available during the period until July, when all non-heat-treated products would be removed and destroyed." The council then drafted the following set of guidelines:

The following groups of individuals should preferentially receive heat-treated products during the changeover period:

- (1) Those previously tested and known to be sero-negative for HTLV-III [HIV].
- (2) Young children.
- (3) Those who have seldom required treatment since 1979.
- (4) Those who are regularly treated with cryoprecipitate and who require factor concentrate for isolated indications, e.g. surgery and travel.

On 19 April 1985, the medical and scientific advisory committee of the Canadian Hemophilia Society met to develop the protocol. Dr Naylor attended the meeting as the Red Cross representative on the committee. He reviewed the Red Cross's implementation plan for distribution of heat-treated concentrates and said that only limited quantities of heat-treated concentrates would be available during May and June, especially during May. Dr Irwin Walker, representing the physicians treating hemophiliacs in Ontario, presented the guidelines that had been developed by the Ontario chapter's advisory council. A discussion of those guidelines followed, which ended with the following recommendations for the national protocol:

The recommendations are to identify individuals to whom preference is to be given during the conversion period.

- (1) Previously untreated or rarely treated patients, who require concentrate therapy during the conversion period.
- (2) Previously treated patients known to be sero-negative for HTLV-III [HIV] antibodies.
- (3) Young children who require concentrate during this period.
- (4) Those regularly treated with cryoprecipitate who require factor concentrate for isolated indications, including major surgery or travel.
- (5) The distribution across the country to be equitable.
- (6) The decision of priorities to be done by Hemophilia Clinic Directors in consultation with CRC BTS [Canadian Red Cross blood transfusion service] Centre Directors (similar to Autoplex protocol).

The next day, 20 April, the medical and scientific advisory committee presented its annual report to the annual general meeting of the Canadian Hemophilia Society. That report contained two recommendations: that the protocol be adopted and that "[t]otal conversion to heat-treated product (July 1st, 1985) should be done immediately." The precise meaning of the second recommendation is unclear, for immediate total conversion would render the protocol unnecessary, its *raison d'être* being the existence of a transitional period. It appears that the advisory committee, at the same meeting at which it created the protocol, decided that it should call for "total conversion," the end of the transitional period, as soon as possible. In any event, the annual general meeting accepted the advisory committee's report and approved both recommendations.

On 29 April, Dr Naylor sent the seventeen local medical directors his second memorandum about the distribution of heat-treated concentrates. The portion relevant to factor VIII concentrate reads:

As of May 1st, 1985, each BTS [blood transfusion service] Centre will be supplied with a limited amount of heat-treated factor VIII concentrate ...

These products are reserved *exclusively* for treatment of those hemophiliac patients that fulfill the criteria established by the National Medical and Scientific Advisory Committee of the Canadian Hemophilia Society ...

It is important that only those patients fulfilling these criteria be issued with heat-treated products.

The majority of hemophilia patients should continue to receive non-heat-treated coagulation factor products until after July 1st, at which time only heat-treated coagulation factor products will be distributed to BTS Centres.

Also attached is an information sheet on the particular heat-treated factor VIII concentrates that will be distributed to your Centre before product prepared from CRCBTS [Canadian Red Cross blood transfusion service] plasma is available ...

Your assistance would be appreciated in transmitting this information to hemophilia treatment centres and physicians. [Emphasis in original.]

The local medical directors were thus expressly instructed that, during the transitional period, heat-treated concentrates were to be distributed exclusively to the hemophiliacs who were given priority under the protocol.

May–June 1985: The national distribution of heat-treated factor VIII concentrate

The transition to heat-treated factor VIII concentrate began on 1 May 1985. By then, 213 days (seven months) had passed since the publication of the Levy article reporting that heat treatment inactivated some retroviruses, and 165 days (between five and six months) had passed since the Bureau of Biologics directed the conversion to heat-treated concentrates.

Although the Red Cross accumulated a substantial inventory of heat-treated factor VIII concentrate during May and June 1985, it adhered to the view that the transitional period was fixed and it did not stop distributing non-heat-treated concentrates from all its blood centres until 1 July 1985.

The particulars of the Red Cross inventory of heat-treated factor VIII concentrate during May and June 1985 that follow are based upon contemporaneous analyses of the national inventory, contemporaneous records of local inventories, and summaries of local inventories prepared for the hearings by the Red Cross. Some of the figures are necessarily approximate. The contemporaneous records and summaries of local inventories are for twelve of the seventeen blood centres. Those centres distributed approximately 80 per cent of all factor VIII concentrate during 1984 and 1985. In the tabulation that follows, it has been assumed that those twelve centres also distributed approximately 80 per cent of the heat-treated factor VIII concentrate during May and June 1985, and the figures from those twelve centres have been prorated to derive total figures for all seventeen centres. In Table 15.1, "received by national" refers to shipments received by the national warehouse

of the Red Cross from manufacturers; "distributed by centres" refers to distributions by the seventeen local blood centres to hospitals, hemophilia treatment centres, physicians, and hemophiliacs; and "total inventory" refers to the stock of heat-treated factor VIII concentrate held by the Red Cross both in its national warehouse and at the local blood centres.

The significance of these quantities is more easily understood if the inventories are expressed as the length of time that it normally would have taken to consume them. The average national consumption of factor VIII concentrate during 1984 and 1985 was approximately 840,000 units per week. By dividing that figure into the estimated inventory for any given date, an estimate is made in Table 15.2 of the Red Cross's ability to meet the national demand for heat-treated concentrates during the transitional period of May and June.

The deliveries of heat-treated concentrates to the Red Cross's national warehouse before July 1985 were somewhat lower than had been expected. Deliveries from Armour were significantly ahead of schedule from 1 May onward, but deliveries from Cutter were significantly behind schedule until mid-June. No point would be served by reviewing the details of early and late deliveries. It is, however, instructive to review their cumulative effect. Taking into account Armour's early deliveries and Cutter's late deliveries, the Red Cross received 6.2 million fewer units than expected by 1 May, 10.2 million fewer units than expected by 1 June, and 3.2 million fewer units

Table 15.1

Estimated deliveries and total inventory (in units) of heat-treated factor VIII concentrate held by the Canadian Red Cross Society, April-June 1984

Date	Supplier	Received by national	Distributed by centres	Total inventory
25 April	Armour	1,635,860		1,635,860
29 April	Cutter	2,577,960		4,213,820
1 May	Armour	3,590,380		7,804,200
1-31 May			approx. 275,000	7,529,000
1-5 June			negligible amount	
5 June	Cutter	7,259,830		14,786,000
6-13 June			approx. 120,000	14,666,000
13 June	Cutter	3,723,440		18,389,000
14-30 June			approx. 840,000	17,550,000

Note: All concentrates were commercial (from plasma secured by the U.S. fractionators) except for the delivery of 13 June, which was custom fractionated from plasma provided by the Canadian Red Cross. Inventories have been rounded to account for approximations.

Table 15.2
Estimated supply, in weeks, of heat-treated factor VIII concentrate held
by the Canadian Red Cross Society, May–June 1985

Date	Inventory (units)	Supply (weeks)
1 May	7,804,200	9.5
1 June	7,529,000	9.0
5 June	14,786,000	17.5
13 June	18,389,000	22.0
30 June	17,550,000	21.0

Note: Supplies have been rounded to the nearest half-week.

than expected by 1 July. Had Cutter met its schedule, the Red Cross would have had enough heat-treated concentrate at the end of the transitional period to meet more than twenty-four weeks of normal demand. The Red Cross expected to receive supplies every month after June 1985 that would be sufficient to meet the monthly demand and to maintain its inventory. Cutter's deliveries were on schedule by mid-July, and thereafter the Red Cross's expectations were met.

After the consensus conference, the Red Cross had continued to receive factor VIII concentrate that was not heat treated. During 11 to 31 December 1984, it received approximately 1.3 million units of non-heat-treated factor VIII concentrate; during January 1985, approximately 4.0 million units; during February 1985, approximately 900,000 units; during March 1985, approximately 800,000 units; and during April 1985, approximately 1.5 million units – a total of approximately 8.5 million units, just over ten weeks' supply. The Red Cross received only heat-treated factor VIII concentrate from fractionators during the transitional period of May–June 1985, and its inventory of non-heat-treated concentrates decreased steadily during those months.

The particulars of the Red Cross's inventory of non-heat-treated factor VIII concentrate during May and June 1985 are known from contemporaneous analyses of the national inventory, contemporaneous records of local inventories, and summaries of local inventories prepared by the Red Cross. The information related to local inventories is for seven centres, which distributed approximately 65 per cent of all factor VIII concentrate during 1984 and 1985. In Table 15.3, it has been assumed that those seven centres also distributed approximately 65 per cent of the non-heat-treated factor VIII concentrate during May and June 1985, and the figures from them have been prorated to derive total figures for all seventeen centres. Using the same method as that described above, the quantities in inventory have been expressed as the length of time that normally would have been taken to consume them.

Table 15.3
Estimated supply, in weeks, of factor VIII concentrate held by
the Canadian Red Cross Society, May–June 1985

Date	Non-heat-treated (weeks)	Heat-treated (weeks)
1 May	5.0	9.5
15 May	3.5	9.0
1 June	1.5	9.0
5 June	1.0	17.5
13 June	0.6	22.0
30 June	0.1	21.0

Note: Supplies have been rounded to the nearest half-week when greater than one week and to the nearest one-tenth of a week when less than one week.

The amounts of the two types of concentrate distributed by the blood centres during the transitional period can also be expressed as the lengths of time it normally would have taken to consume them. During May and June 1985, the centres collectively distributed five weeks' supply of non-heat-treated factor VIII concentrate. During the same period, they distributed one to two weeks' supply of heat-treated factor VIII concentrate, all but three days' supply of which was distributed after 13 June. Even then, the centres continued to distribute non-heat-treated concentrates until there was only one day's supply left throughout Canada.

It is useful to review the statements made by the national office of the Red Cross blood transfusion service, externally to the Canadian Hemophilia Society and internally to the local medical directors, during the transitional period of May and June while the inventory of heat-treated factor VIII concentrate was increasing. On 28 May, with approximately nine weeks' supply of heat-treated factor VIII concentrate in stock, Dr Perrault responded to a letter sent to Dr Naylor by the Canadian Hemophilia Society after its annual general meeting. That letter had attached to it the society's recommendation that "[t]otal conversion to heat-treated product (July 1st, 1985) should be done immediately." When Dr Naylor forwarded the letter to Dr Perrault, he reminded him that immediate conversion was "not possible." In his response, Dr Perrault wrote:

With respect to distribution of heat-treated coagulation factor products, as you will recall, the CRCBTS [Canadian Red Cross blood transfusion service] assisted the CBC [Canadian Blood Committee] in planning the

December 10th, 1984 consensus conference at which it was agreed that distribution of these products would begin on May 1st, 1985, with complete conversion by July 1st.

This timetable will be met. On May 1st, the CRCBTS distributed limited supplies of heat-treated factor VIII to all BTS Centres. Only heat-treated products will be distributed after July 1st.

Two days later, on 30 May, Dr Naylor sent the seventeen local medical directors his third memorandum about the distribution of heat-treated concentrates. With respect to factor VIII concentrate, it reads, in part:

Full conversion to distribution of heat-treated coagulation factors should occur in the last two weeks of June.

In the meantime, to enable an equitable and uninterrupted conversion, routine Centre requirements for factor VIII concentrate can only be met with untreated products. This is because there is currently an insufficient supply of the heat-treated products to fill all routine requests.

To facilitate the conversion in your region, the remaining inventory of the heat-treated product at National has been allocated to all Centres. Supplies (sufficient for approximately 2 weeks) will be shipped to your Centre in the week of June 10th.

The words "uninterrupted conversion" in this memorandum are a key to understanding Red Cross thinking during May and June 1985. The managers of the blood transfusion service believed that the inventory of heat-treated factor VIII concentrate would be secure only when it reached a level that ensured that no hemophiliac with priority under the protocol would have to use non-heat-treated concentrates. Dr Perrault and Dr Davey testified that they believed that the provision of heat-treated factor VIII concentrate on a "continual basis" was the commitment given by the Red Cross at the consensus conference, and that it captured the spirit of the agreement reached at the conference.

Dr Langley and Dr Koopmann, members of the advisory subcommittee of the Canadian Blood Committee who had participated at the consensus conference, testified that they did not agree with the view expressed by Dr Perrault and Dr Davey about the understanding that had been reached at that conference. Dr Langley, who represented the Canadian Cancer Society at the conference, stated:

The ethical decisions that had to be made, it was agreed, would be made between the doctor and the patient, not by some bureaucrat in an office, about whether I will or will not provide it [heat-treated concentrate]. I mean, I don't think Dr Davey should have made that decision.

Dr Koopmann, who represented the Canadian Medical Association, agreed with Dr Langley and added:

The consensus conference said, "as soon as possible," or "feasible," "before May." In other words, we [treating physicians] would get the stuff and we would use it, as soon as feasible, as soon as possible.

Dr Inwood testified to the same effect and said that it had been agreed at the consensus conference that the heat-treated concentrates were "to be distributed immediately, as soon as feasible."

On 20 June, with twenty-one to twenty-two weeks' supply of heat-treated factor VIII concentrate in stock, Dr Naylor sent the seventeen local medical directors his fourth memorandum about the distribution of heat-treated concentrates. It reads as follows:

Further to my memo of May 30, 1985 this is to advise you on the actions to be taken during the upcoming six week period.

- a. National will ship to all Centres a further two week supply of heat-treated factor VIII concentrate and a one month supply of heat-treated factor IX concentrate in the week of June 24th.
- b. All Centres are to issue only the heat-treated products effective 1 July.
- c. All non-heat-treated factor VIII and factor IX concentrate is to be withdrawn from hospital inventories and hemophiliacs' home inventories ...

Projected deliveries still indicate that there will be sufficient amounts of heat-treated coagulation factor product available to meet routine demands over the summer and to maintain emergency reserves at National Office.

By 1 July 1985, 274 days (nine months) had passed since the publication of the Levy article reporting that heat treatment inactivated some retroviruses, and 226 days (seven and a half months) since the Bureau of Biologics's directive recommending the conversion to heat-treated concentrates.

Red Cross concern about financial consequences

On 20 June 1985, as the transitional period was about to end, one of Dr Naylor's assistants wrote a memorandum about the non-heat-treated factor concentrates that he estimated would be left after the transitional period:

Estimated CRC [Canadian Red Cross] Inventories 1 July, 1985:

- a. Factor VIII Concentrate: Based on previous projections of inventories of this product going to zero by June 17th, and the knowledge that not all Centres have cooperated fully in the final distribution of this product

it is estimated that the final inventory in CRC hands will be approximately 500,000 AHF [anti-hemophilic factor] units. The write-off will therefore be approximately \$50,000.

- b. Factor IX Concentrate: Currently, there are approximately 10,000 vials of factor IX remaining in inventory. Levels are not expected to change significantly in the next week. The write-off will therefore be approximately \$200,000.

Therefore, the CRC will have a total write-off of approximately \$250,000 due to the withdrawal of these products.

As we have previously discussed, this write-off was a "given" when the decision was made to introduce the heat-treated product in December 1984.

The memorandum then continued, with regard to the stocks already distributed by the centres but not yet used and held outside the Red Cross:

The question now is "should the CRC credit the hospitals for all product returned."

The answer to this question is complex in that product may have been issued several months ago, but may have been sitting on hospital shelves or in hemophiliacs' homes, unused, waiting for the introduction of the heat-treated products. Furthermore, it is impossible to estimate how much product this represents and the resultant dollar value of any write-off required.

The CRC must, therefore, decide on the most appropriate course of action from the three options available:

- a. credit the provinces for all product returned;
- b. credit the provinces for no product returned;
- c. credit the provinces for a portion of product returned.

Option a) could create serious cash flow problems for the programme.

Option b) while the best for the CRC cash position would place the CRC in a position whereby the provinces could imply we had dumped product into the hospitals to cut losses.

Option c) would appear to be the best compromise as the CRC will be in a position to define the amount of the product that will be accepted for credit and identify the cost implications.

The concerns expressed in this memorandum – that "the CRC will have a total write-off" and that "the provinces could imply we had dumped product into the hospitals to cut losses" – reflect a belief that the Red Cross faced a financial risk because of unused concentrate.

On 24 June 1985, in a memorandum to Dr Davey, Dr Naylor expressed a similar concern:

Ultimately, it is assumed that the costs associated with writing off the costs of returned non-heat-treated coagulation factor products will be supported by the provinces. However, if the CRCBTS [Canadian Red Cross blood transfusion service] is to credit provinces for all product returned, a cash flow squeeze could occur and special arrangements would have to be made to support such a course. Alternatively ... if no credit is given for product returned, it could be implied that the CRCBTS had tried to minimize its write-off losses by distributing its inventory to hospitals before the conversion to heat-treated products.

Again, the concern that "it could be implied that the CRCBTS had tried to minimize its write-off losses by distributing its inventory" demonstrates that Dr Naylor also believed that the Red Cross faced a financial risk.

Several months later, the most senior Red Cross officers were still concerned about possible financial loss from unused inventory of non-heat-treated concentrates. In a memorandum to Dr Perrault dated 21 November 1985, the secretary general, George Weber, said that both he and the president wanted to know the answer to the question, "[I]s the CBC [Canadian Blood Committee] going to cover it?" On 2 December, Dr Perrault replied that a letter had been written to the Canadian Blood Committee asking it to write off the cost of the unused inventory and that the reply had not yet been received.

Claude Morin, who was the national administrator of the blood transfusion service in 1985, and in that capacity was responsible for its financial affairs, testified that, given the arrangement between the Red Cross and the Canadian Blood Committee with regard to the cost of blood products, the Red Cross had never been at risk of losses from undistributed inventory. The arrangement was that the provinces paid a price for blood products that was higher than the price paid by the Red Cross to manufacturers, the surplus being accumulated in the Red Cross's fractionation account. These funds, held in trust by the Red Cross, were the property of the provinces, and were kept separate from other Red Cross funds. The Red Cross billed all fractionation-related expenses (for example, for manufacturing, transportation, and financing) to the provinces and withdrew the appropriate amounts from the fractionation account. All fractionation-related costs incurred by the Red Cross were to be reimbursed. Mr Morin testified that the memoranda quoted above left the impression that the writers had erroneously believed that there was a risk of financial loss, although they should have known that there was no risk.

Six months after the conversion to heat-treated factor concentrates had been completed, the Canadian Blood Committee, at a meeting on 16–17 December 1985, considered the question of the unused concentrate.

The financial analyst in the committee's secretariat wrote a background memorandum that contained the following opinion:

The cost of the unusable non-heat-treated factor VIII and IX is a Blood Programme cost and hence a funding responsibility of the CBC [Canadian Blood Committee] funding governments (barring negligence or mismanagement at the Society).

Attached to the memorandum was a Red Cross position paper in which the blood transfusion service described its management of the conversion to heat-treated concentrates and explained why it was not responsible for the cost of unused concentrate. The Canadian Blood Committee decided to write off the cost of the unused concentrate.

May–June 1985: Distribution by the local centres of heat-treated factor VIII concentrate

For the local officials in charge of the distribution of factor concentrates, Dr Naylor's memoranda were the principal source of information about the state of the Red Cross's inventory during May and June. Although parts of Dr Naylor's four memoranda have already been presented, it is helpful to repeat the portions of them that are relevant.

Dr Naylor's 20 March memorandum reads, in part:

During the period May 1st to July 1st, 1985, limited amounts of heat-treated factor VIII concentrate and factor IX complex will be distributed to BTS [blood transfusion service] Centres. The greater proportion of coagulation factor products will continue to be supplied in non-heated form during this transition period ...

During the transition period May 1st–July 1st, all Centres will receive small amounts of heat-treated factor VIII and factor IX that will be a proportion of their normal monthly utilization; this proportion will be determined according to the estimated number of patients that are eligible to receive heat-treated products preferentially according to the criteria that will be established at the April 19th meeting of the CHS MSAC [Canadian Hemophilia Society medical and scientific advisory committee].

The medical directors were told, more than a month before any heat-treated concentrates were to be distributed and before the national office had received any heat-treated concentrates from the fractionators, to expect shortages of the new, heat-treated concentrates throughout the transitional period. The local officials had experienced shortages of factor VIII concentrate over the previous two years. They were therefore accustomed to managing their

local inventories during times of shortage, and would have had no reason to question the information that shortages of the new concentrates would be the order of the day throughout the transitional period.

Dr Naylor's 29 April memorandum reads, in part: "As of May 1st, 1985, each BTS Centre will be supplied with a limited amount of heat-treated factor VIII concentrate." As in the memorandum of 20 March, the medical directors were told to expect shortages during the transitional period.

Dr Naylor's 30 May memorandum reads, in part:

Full conversion to distribution of heat-treated coagulation factors should occur in the last two weeks of June.

In the meantime, to enable an equitable and uninterrupted conversion, routine Centre requirements for Factor VIII concentrate can only be met with untreated products. This is because there is currently an insufficient supply of the heat-treated products to fill all routine requests.

The medical directors were thus expressly informed, halfway through the transitional period, that it would have to be extended because there was not enough heat-treated factor VIII concentrate for all hemophiliacs.

Dr Naylor's 20 June memorandum reads, in part:

Further to my memo of May 30, 1985 this is to advise you on the actions to be taken during the upcoming six week period.

- a. National will ship to all Centres a further two week supply of heat-treated factor VIII concentrate and a one month supply of heat-treated factor IX concentrate in the week of June 24th ...

Projected deliveries still indicate that there will be sufficient amounts of heat-treated coagulation factor product available to meet routine demands over the summer and to maintain emergency reserves at National Office.

Although dated 20 June, this memorandum was not received by most of, if not all, the medical directors until the following week.

The issue of local inventory management during the transitional period was not investigated in the hearings at which the events at the blood centres in Vancouver, Calgary, and Edmonton were reviewed. Thereafter, the issue was examined for all the remaining local blood centres, with the exception of Ottawa and Sudbury.

The particulars that follow in Table 15.4 of the local inventories of factor VIII concentrate during May and June, for the twelve centres that were examined, are based on contemporaneous records of local inventories and the summaries of local inventories prepared by the Red Cross. For some centres the information was incomplete. "Received" refers to receipts of concentrates by the centres from the national warehouse; "distributed" refers to distributions

Table 15.4
Inventory of heat-treated and non-heat-treated factor VIII
concentrates at twelve Red Cross blood centres, May-June 1985

Date (1985)	Heat-treated			Non-heat-treated	
	Received (units x 1,000)	Distributed (units x 1,000)	Inventory (in weeks)	Inventory (in weeks)	Reissued (units x 1,000)
<i>Charlottetown centre</i>					
30 April	9.3				
1 May			1.0	NA	
11 June	21.7		4.0	NA	
24 June	28.8		8.0	NA	
30 June			8.0	0.8	
<i>Halifax centre</i>					
30 April	15.5				
1 May			0.9	5.0	
12 June	41.9		3.5	0.9	
14 June			3.5	0.0	
17-20 June		20.2	2.5	0.0	
24-25 June		13.0	1.5	0.0	7.2
26 June	51.2		4.5	0.0	
26-28 June		19.8	3.5	0.0	
30 June			3.5	0.0	
<i>Hamilton centre</i>					
30 April	32.8				
1 May			0.5	1.5	
6-9 May		14.0	0.3	2.5	
13 May	31.0	31.0	0.3	2.0	
14 May	229.8		3.5	1.5	
30 May			3.5	0.5	
31 May	32.8		4.0	0.7	
5 June			4.0	0.5	
6 June			4.0	1.0	
10 June	138.8	10.3	6.0	0.6	
11-18 June		9.1	5.5	0.1	
19 June		5.7	5.5	0.0	
20-24 June		20.5	5.0	0.0	
25 June		15.8	5.0	0.0	1.1
26 June	12.8	15.6	6.5	0.0	
27 June		43.7	6.0	0.0	2.3
28 June		5.4	6.0	0.0	
30 June			6.0	0.0	

Table 15.4 (cont'd)

Date (1985)	Heat-treated			Non-heat-treated	
	Received (units x 1,000)	Distributed (units x 1,000)	Inventory (in weeks)	Inventory (in weeks)	Reissued (units x 1,000)
<i>London centre</i>					
30 April	25.7				
1 May			0.5	2.5	
2 May	31.4		1.0	2.0	
7 May		15.7	0.8	1.5	
8 May			0.8	1.5	
9 May		11.4	0.5	2.5	
24 May		1.7	0.5	0.8	
27 May			0.5	2.0	
3 June		1.7	0.5	0.2	
4 June			0.5	1.5	
10 June		5.7	0.4	1.5	
11 June	99.2		2.0	1.0	
24 June		14.5	2.0	0.5	
25 June	85.5	4.3	3.5	0.5	
30 June			3.5	0.2	
<i>Montreal centre</i>					
30 April	201.5				
1 May			1.0	2.5	
15 May			1.0	0.8	
16 May			1.0	2.0	
27 May		7.5	0.9	2.5	
7 June	372.0	22.3	2.5	1.0	
14 June			2.5	0.0	
18–21 June		44.6	2.5	0.0	
24 June	252.0		NA	0.0	
30 June			NA	0.0	
<i>Quebec City centre</i>					
30 April	62.0				
1 May		62.0	0	NA	
11 June	114.7		2.0	NA	
22 June			2.0	0.0	
24 June	139.5		NA	0.0	
30 June			NA	0.0	

Table 15.4 (cont'd)

Date (1985)	Heat-treated			Non-heat-treated	
	Received (units x 1,000)	Distributed (units x 1,000)	Inventory (in weeks)	Inventory (in weeks)	Reissued (units x 1,000)
<i>Regina centre</i>					
30 April	6.2				
1 May			0.9	NA	
12 June	15.5		3.0	NA	
14-17 June		12.1	1.5	NA	
24 June	20.2	2.5	4.0	0.0	
25 June		3.1	3.5	0.0	
30 June			3.5	0.0	
<i>Saint John centre</i>					
1 May	49.6		1.0	3.0	
13 May			1.0	1.5	
14 May			1.0	3.0	
27 May			1.0	1.0	
28 May			1.0	1.5	
13 June	114.7		4.0	0.6	
25 June		31.3	3.5	0.0	
26 June	139.5		6.5	0.0	
26-30 June		16.7	6.5	0.0	10.4
<i>St John's centre</i>					
1 May	24.8	14.9	0.4	NA	
6 May		7.4	0.1	NA	
13 June	58.9	58.9	0.1	NA	
26 June	69.8		3.0	NA	
30 June			3.0	1.5	
<i>Saskatoon centre</i>					
1 May	24.8		1.5	NA	
12 June	49.6		4.0	NA	
21 June		12.4	3.5	0.0	
26 June	62.0		7.0	0.0	
27-28 June		16.1	6.0	0.0	
30 June			6.0	0.0	

Table 15.4 (cont'd)

Date (1985)	Heat-treated		Non-heat-treated	
	Received (units x 1,000)	Distributed (units x 1,000)	Inventory (in weeks)	Reissued (units x 1,000)
<i>Toronto centre</i>				
29 April	114.9			
1 May			0.8	1.2
4 May		57.0	0.4	0.9
6 May			0.4	0.8
7 May			0.4	1.2
12 May			0.4	1.0
13 May			0.4	1.3
16 May			0.4	0.4
17 May			0.4	0.9
21 May			0.4	0.8
22 May			0.4	1.3
26 May			0.4	0.4
27 May			0.4	0.7
29 May		1.4	0.4	0.9
30 May			0.4	1.0
7 June	79.6		1.0	0.3
13 June		46.5	0.6	0.3
14 June			0.6	0.4
21 June		2.8	0.6	0.0
24 June	169.5		1.9	0.0
25-27 June		120.0	1.0	0.0
28 June	108.5	108.5	1.0	0.0
29-30 June		22.6	0.8	0.0

Table 15.4 (concluded)

Date (1985)	Heat-treated			Non-heat-treated	
	Received (units x 1,000)	Distributed (units x 1,000)	Inventory (in weeks)	Inventory (in weeks)	Reissued (units x 1,000)
<i>Winnipeg centre</i>					
30 April	40.3				
1 May			1.0	3.0	
3 June			1.0	0.9	
4 June			1.0	1.5	
8 June		1.2	1.0	1.0	
12 June	69.8		3.5	0.7	
20 June		1.2	3.0	0.4	
25 June	89.9		6.0	0.1	
30 June		2.2	6.0	0.1	

Note 1: For all centres but Toronto, supplies have been rounded to the nearest half-week when the inventory was greater than one week's supply and to the nearest one-tenth of a week when the inventory was less than one week's supply. For the Toronto centre, all supplies have been rounded to the nearest one-tenth of a week.

Note 2: Non-heat-treated units that were reissued were received and redistributed on the same day or within the days shown and do not appear in inventory.

by the centres to hospitals, hemophilia treatment centres, physicians, and hemophiliacs; "reissued" refers to the redistribution of concentrates that were returned to the centres; "inventory" refers to the inventory held in the centres. As was true of inventory figures given earlier, the local inventory figures are more easily understood and compared if expressed as the length of time that it normally would have taken to consume them. In order to calculate these lengths of time, the inventory in each centre was divided by the average weekly local consumption of factor VIII concentrate at that centre during 1984 and 1985. For example, the average weekly consumption of factor VIII concentrate distributed by the Charlottetown blood centre was approximately 7,600 units, and the thirty vials held on 30 April contained 9,300 units; 9,300 units divided by 7,600 units per week equals 1.22 weeks, which has been rounded to 1 week.

As will be evident from the table, responses to the availability of heat-treated concentrates varied considerably from centre to centre. Some followed the transitional schedule rigidly. Some distributed non-heat-treated concentrates until their supply was exhausted, and in a few cases subsequently reissued non-heat-treated concentrates that had been returned to them. Others chose to distribute heat-treated concentrates soon after receiving them.

The Charlottetown blood centre distributed no heat-treated concentrate before 1 July 1985, by which time it had approximately eight weeks' inventory on hand. The deputy medical director of the centre, who was also a physician who treated hemophiliacs, testified that she held the local inventory of heat-treated concentrates in reserve in case a person with priority under the protocol needed it.

At the Halifax centre, the inventory of non-heat-treated concentrates was exhausted on 14 June. Thereafter, with one exception, all distribution was of heat-treated concentrates. The exception occurred on 24 and 25 June, when the centre reissued 7,200 units (contained in thirty-four vials) of non-heat-treated concentrates that had been returned to it. The medical director explained in his testimony:

Those went to [a] patient ... who was a severe hemophiliac, who in the interim between June 3 and June 13 had required 91 vials for treatment of a severe bleed. There was an indication that he might bleed again. He was a candidate specifically, since we had knowledge of his treatment course because he was so severe on occasion and had received non-heat-treated material over a long period of time, and he was, under the guidelines, an appropriate candidate for non-heat-treated material.

Because we had no other in inventory as of June 14, these were the only non-heat-treated materials that we had available to send out. That was under the guidelines. It did protect the inventory of heat-treated material for, as we said before, the requirements for those who were listed under the Canadian Hemophilia Society prioritization.

At the Hamilton centre, the inventory of non-heat-treated concentrates was exhausted on 19 June. All distribution thereafter was of heat-treated concentrates except on 25 and 27 June, when a total of 3,400 units (thirteen vials) of non-heat-treated concentrates that had been returned to the centre were reissued. At that time, the centre had roughly six weeks' supply of heat-treated concentrates in stock. At the hearings, the medical director was asked why the non-heat-treated products were reissued. He explained:

- A. What appears to have happened, or my recollection as to what happened is that I did not take care in the Centre to instruct them not to re-issue returns. What they were doing was following standard instructions about making sure that the appropriate issues could take place based on instructions that had occurred previously. It was not my instruction. I did not give an instruction specifically to issue those returned vials on the specific dates as late as June 27. I don't recall being even asked about them.

- Q. Should you have instructed your staff not to re-issue those things that were returned?
- A. In retrospect, based on the information that is available to us now, my answer would have to be "yes."

The London centre distributed 36,200 units (127 vials) of heat-treated concentrate between 7 May and 10 June, and another 18,800 units (sixty-six vials) on 24 and 25 June. Then, between 26 and 28 June, when it had approximately three and one-half weeks' inventory of heat-treated concentrates, it distributed approximately 12,500 units (fifty vials) of non-heat-treated concentrate that it still had in stock. The medical director explained in testimony that the heat-treated concentrates were not distributed during that time because "it was our anticipation that that was basically a supply for July."

The Montreal centre distributed 7,500 units (twenty-four vials) and 22,300 units (seventy-two vials) of heat-treated concentrate on, respectively, 27 May and 7 June. The supply of non-heat-treated concentrates was exhausted on 14 June, and only heat-treated concentrates were distributed thereafter.

In Quebec City, the local blood centre delivered all its first shipment of heat-treated concentrate to the local hemophilia treatment centre the day after it was received. The hemophilia centre was aware that the blood centre received a large quantity of heat-treated factor VIII concentrate on 11 June. The treatment centre did not order any of it from the blood centre during 11–22 June. By 22 June, the local supply of non-heat-treated factor VIII concentrate was exhausted, and distribution thereafter was of the heat-treated product.

The Regina centre distributed a mixture of heat-treated and non-heat-treated concentrates from 14 to 24 June, when the inventory of non-heat-treated concentrate was exhausted. It received no requests for concentrates under the protocol during that time. The medical director of the centre testified:

[W]e were under specific instructions not to distribute any heat-treated product. It was to be used exclusively for those patients that fit the MSAC [medical and scientific advisory committee] guidelines up until June [sic, for July] 1. At this point in time, in the middle of June, we decided we would take a chance, if you like, and having this inventory in Centre wasn't doing us any good. We decided to start shipping out to [treatment] centres and we departed from the guidelines we were told to follow.

At the Saint John centre, the inventory of non-heat-treated concentrates was exhausted on 25 June. During the rest of the month, 10,400 units (forty-six vials) of non-heat-treated concentrate that had been returned to the centre were reissued. Otherwise, all concentrates distributed after 25 June were heat treated. At the hearings, the centre's medical director was asked why

heat-treated concentrates had not been distributed earlier. He replied, "Because we were under instructions to reserve heat-treated product for particular indications." The following exchange occurred:

- Q. So, despite the fact that there weren't supply concerns and despite the fact that there were definite safety concerns, it was much more important to follow a strict guideline that you couldn't release something until the next day.
- A. I think the short answer is: Yes, it is. We follow guidelines. Number two, we assume that the treating physician is familiar with the priorities established by the Canadian Hemophilia Society as to who should receive what product.

Later:

- A. As part of a national organization responsible for a great many people, a decision was made that we would hold in reserve this new product in the event that it was required by one of those people designated by the Canadian Hemophilia Society to get preferential treatment in case one of those people should have needed that supply.
- Q. In the last five days of June ... there was no risk that you were going to run out of heat-treated factor VIII for any priority list. You had more than 700 vials on your shelf. There is not one day in the two months that we have before us that your laboratory was ever asked for 700 vials in one day. So the priority list does not come into play in the last five days of June, does it? ...
- A. Because we never know at what time we would be called upon to supply a large amount of factor for someone who is injured, who has had a sudden hemorrhage, who has had some sort of trauma. The average distribution is just that. It is an average. It provides no guarantee whatsoever that we will not be required to use 700 or a great deal more than 700 in the last hours, minutes, or seconds.

The St John's centre, which received 24,800 units (eighty vials) of heat-treated concentrate on 1 May, distributed 14,900 units (forty-eight vials) the same day and another 7,400 units (twenty-four vials) on 6 May. It received 58,900 units (190 vials) on 13 June and distributed them the same day. The medical director explained in his testimony:

I am very fortunate that our staff are not good, our staff are magnificent, and I think the province should be proud of the BTS [blood transfusion

service] staff in this province. I delegate to people with total confidence. They are that good. And I could not do it all myself if I tried.

One of these people was the laboratory supervisor [Tom Peddle] who had always handled the distribution of Factor VIII, so he was made aware of these memoranda [from Dr Naylor] ...

It was only a few weeks ago, but I actually enquired what happened. He said, "As they came in, I gave them to the hemophilia treatment centre." I said, "Thank you, Mr Peddle." I felt like dropping on my knees to say thank you, but I didn't.

He in fact did what should have been done. He said to the treaters, "This is your problem. It's not mine." That's what he actually did. But I did not know at the time that he had done this.

I'm not even sure if I was in personal charge what I would have done. I was under the impression right up to late June that this product was in desperately short supply. It may be, it may not. I do not know. Therefore I would have been much more tempted to have followed the protocol up to 11:59 p.m. on June 30. That could have been argued was the right thing to do under the circumstances of this incredible shortness of this product, and, if we break the rules there would be nothing in July. That was the message handed down.

But Tom Peddle decided, actually without my knowledge, to say, "This is not the job of the Red Cross. This is the hemophilia comprehensive treatment centre's job."

He kept eight vials. I asked why. And [he said], "If there was a sudden strange event, it might sort of cope."

As it turned out, I thanked him for disobeying a string of instructions.

At the Saskatoon centre, the inventory of non-heat-treated concentrates was exhausted by 21 June, and after that date only heat-treated concentrates were distributed. No heat-treated concentrates were distributed before then.

The Toronto centre distributed 58,400 units (205 vials), roughly half its stock of heat-treated concentrates, during May, and a further 49,300 units (173 vials) during the first two weeks of June. During May and June, the centre never had more than 1.3 weeks' supply of non-heat-treated concentrate in stock. The national warehouse was located in Toronto, however, and on eight occasions from 7 May to 14 June (at which time its stock of non-heat-treated concentrate was exhausted) the national warehouse replenished the local centre's stock of non-heat-treated concentrates. The Toronto centre's inventory of non-heat-treated concentrates was exhausted on 21 June, and all concentrates that it distributed thereafter were heat treated.

At the Winnipeg centre, 1,240 units (four vials) of heat-treated concentrate were distributed on 8 June, and another 1,240 units (again four vials) on 20 June, for treatment of a patient with priority under the protocol. After 25 June, only heat-treated concentrates were distributed.

In summary, some blood centres reissued non-heat-treated factor VIII concentrate that had been returned to them after they had significant local inventories of heat-treated concentrates (as much as seven weeks' supply) and some centres distributed no heat-treated concentrate, or very little, even after they held significant local inventories (as much as eight weeks' supply). The impact of these actions was to reduce the total blood transfusion service's inventory of non-heat-treated factor VIII concentrate to one day's national supply. At the end of 30 June, according to statistics gathered by the national office, 75 per cent of that one day's supply was held in three centres, those in Calgary, Edmonton, and St John's; the remaining 25 per cent was held in the Charlottetown, London, Winnipeg, and Vancouver centres.

The local blood centre officials had been led to believe by the national office of the blood transfusion service that heat-treated concentrates were in short supply at the national warehouse. As a result, some medical directors were concerned that, unless they followed the directions of the national office strictly, they would not be able to meet the needs of a hemophiliac with priority under the protocol who might require large amounts of concentrate. Others were concerned that, unless they followed the directions of the national office strictly, they might have no factor VIII concentrate later that summer. The medical directors did not take, or instruct others to take, the actions described in order to exhaust the national inventory of non-heat-treated concentrate.

Factor IX: The production, approval, and distribution of heat-treated concentrates

Factor IX concentrate, unlike factor VIII concentrate, was not in chronic short supply in the mid-1980s. The Red Cross was able to meet the needs of all type B hemophiliacs from custom fractionation of the plasma it collected. The Red Cross's Canadian fractionator, Connaught, was not licensed to manufacture heat-treated factor IX concentrate during 1984 and 1985; the timing of the conversion to heat-treated factor IX concentrate in Canada depended therefore on the speed with which the Red Cross's U.S. custom fractionator, Cutter, could produce it and secure regulatory approval for its distribution.

The production of heat-treated factor IX concentrate was less complicated than the production of heat-treated factor VIII concentrate. Factor VIII concentrate production required an extra step early in the process to prevent a loss of activity in the factor VIII during heating. Factor IX concentrate, in contrast, could be heated without additional processing. Approximately five months' supply of heat-treated factor IX concentrate had been produced from Canadian plasma even before the consensus conference took place on 10 December 1984. The Red Cross had directed Cutter on 26 November to heat treat all factor IX concentrate being made from plasma collected by the Red Cross. Only eight days later, on 4 December, Cutter reported that it had successfully heat treated 10,000 vials. The Red Cross's memorandum of a meeting with Cutter that day records that 10,000 vials of factor IX were available, and adds that

these "product lots will be returned at a time coinciding with first deliveries of treated factor VIII concentrates." All that was needed to begin distribution was approval by the regulatory authorities.

Although the consensus conference made no express recommendations about factor IX concentrate, the Red Cross presentations contained two references to them. Dr Davey said:

Sufficient [factor] IX concentrate to meet Canadian needs can easily be produced from plasma of Canadian origin. It is already known that such concentrates can be pasteurized without loss of activity and at little extra cost. Subject to licensing by Canadian BoB [Bureau of Biologics], it will be possible to introduce heat-treated [factor] IX concentrates in Canada at the same time as the new factor VIII preparations. There will therefore be no further reference to factor IX concentrates in these submissions.

Dr Naylor said:

With the rather complex logistics of ensuring continuity of supplies of essential blood products, it is not surprising that implementation of heat-treated coagulation factor products presents a particular challenge.

Because it is hoped that these [heat-treated] products will offer a safer means of hemophilia therapy, hemophilia patients will want to use these as soon as possible in preference to untreated coagulation factor preparations. Consequently, the introduction of their distribution must be done in a fair and equitable way across the country, as soon as is feasible.

The fairest way in which this can be achieved is to coordinate the introduction of heat-treated factor VIII and factor IX concentrates at more or less the same time all across the country.

There was no reference to the 10,000 vials that had already been produced.

Regulatory approval to distribute Cutter's heat-treated factor IX concentrate proved far more complicated than its production. In particular, it took longer than expected to obtain approval of the product labelling – the information contained on the vial labels, the boxes in which the vials were packaged, and the product inserts (the printed material accompanying the vials that contained details about the therapeutic benefits and potential risks of the product).

A U.S. fractionator who wanted to deliver a blood product to the Red Cross needed the approval of two regulatory authorities, the Bureau of Biologics in Canada and the Office of Biologics in the United States. U.S. approval was needed even for products custom fractionated for the Canadian Red Cross from Canadian plasma that would be distributed only in Canada. Both regulatory authorities had to license the blood product and approve the labelling for it.

Cutter encountered difficulty in gaining regulatory approval from the U.S. Food and Drug Administration for the labelling of its heat-treated factor IX concentrate for export to Canada, even though the administration had licensed the product for distribution in the United States. The problem was described in a letter from the Red Cross to the Bureau of Biologics dated 26 February 1985, almost three months after Cutter had heat treated the 10,000 vials. The factor IX concentrates that were distributed by the Red Cross at that time were in fact complexes of several coagulation factors found in plasma. The letter said that the Red Cross might in the future distribute two differently constituted factor IX complexes (one, Cutter's product, containing factors II, IX, and X; the other, made by another manufacturer, containing factors II, VII, IX, and X) and a pure factor IX. The Red Cross wanted the labelling for Cutter's product to list the coagulation factors it contained, so that anyone prescribing or using it would be able to distinguish its contents from those of either of the other two factor IX products under consideration. The Office of Biologics did not allow such labelling.

On 10 April 1985, the Bureau of Biologics issued the licence for Cutter's heat-treated factor IX concentrate. This licence allowed the Red Cross to import and distribute the concentrate in Canada. By 14 May, the Office of Biologics, which had licensed Cutter's heat-treated factor IX concentrate in October 1984, approved the listing of the factor components on concentrate that was to be sold to the Canadian Red Cross. This approval allowed Cutter to export the concentrate to Canada.

The Red Cross interpreted the recommendations of the consensus conference as applying to both factor VIII and factor IX concentrates. When Dr Naylor sent the first in his series of memoranda about the conversion to the seventeen local medical directors on 20 March 1985, he treated the two products in the same way, and said he expected to be able to supply the local centres with some heat-treated factor IX by 1 May 1985.

The protocol that established priorities for the distribution of heat-treated concentrates during the transitional period also did not distinguish between factor VIII and factor IX concentrates. As drafted by the medical and scientific advisory committee of the Canadian Hemophilia Society on 19 April, the protocol simply referred to factor concentrates in the plural.

The first time that the conversion to heat-treated factor IX concentrate was treated differently from the conversion to heat-treated factor VIII concentrate was when Dr Naylor sent his second memorandum to the medical directors on 29 April 1985. In it he said:

As of May 1st, 1985, each BTS [blood transfusion service] Centre will be supplied with a limited amount of heat-treated factor VIII concentrate.

Limited amounts of heat-treated factor IX complex will be available on request from Blood Product Services.

Dr Naylor went on to say that, for both products, the heat-treated form was "to be reserved exclusively" for hemophiliacs who met the criteria established by the medical and scientific advisory committee of the Canadian Hemophilia Society.

On 21 May 1985, Cutter shipped the first heat-treated factor IX concentrate to the Red Cross. It was received nine days later, on 30 May. The Red Cross now had 3,753 vials of heat-treated factor IX concentrate in stock, approximately eight weeks' supply.

On the same day, 30 May, Dr Naylor sent the third of his memoranda to the medical directors. In it, he said:

Limited supplies of heat-treated factor IX concentrate are available from the National BTS [blood transfusion service] Office and it is anticipated that inventories of this product will be stabilized by mid-August. To ensure no shortages occur please follow the same procedure outlined for factor VIII concentrate.

No change was made to the plan to hold the heat-treated factor IX concentrate centrally.

On 20 June, Dr Naylor told the medical directors, in his fourth memorandum about conversion, that the national office would ship one month's supply of heat-treated factor IX concentrate to each of the centres during the following week. On 24 June, every centre was sent its first substantial shipment.

Dr Davey testified about the decision not to distribute heat-treated factor IX concentrate to the centres before 24 June. He said:

[S]tock would be held at National Office and distributed to meet specific requirements. This, because the stock at the time was not – was regarded as too limited to decentralize. We would, in fact, have had to distribute virtually all of it to give each Centre a useful stock ...

Well, I believe that Dr Naylor didn't want to see the national warehouse stocked out, and unable to meet emergency orders. Factor IX deficiency, of course, is less common than hemophilia A, and because it is less common, the demand for this product is intermittent and not as predictable, either as to amount or location, as factor VIII.

Asked how long distribution from Toronto to other centres normally took, Dr Davey answered, "routinely deliveries could be made within twenty-four hours."

On 3 and 8 July, the Red Cross received another 9,363 vials of heat-treated factor IX concentrate, approximately nineteen weeks' additional supply.

June–July 1985: The withdrawal of non-heat-treated concentrates

On 20 June 1985, in his fourth memorandum to the medical directors about the conversion to heat-treated concentrates, Dr Naylor gave the following instructions:

All non-heat-treated factor VIII and factor IX concentrate is to be withdrawn from hospital inventories and hemophiliacs' home inventories. Return of the non-heat-treated products to BTS [blood transfusion service] Centres must be completed by July 31st.

The Red Cross had no procedure for withdrawing blood products at this time, and no system for classifying the urgency of the withdrawal. It did not normally distribute factor concentrates directly to hemophiliacs; rather, it distributed them to hospitals and clinics, which, in turn, distributed them to hemophiliacs. The line of communication for notification of the withdrawal of non-heat-treated concentrates followed the line of distribution of the concentrates. The local blood centres notified the hospitals and clinics that had received non-heat-treated concentrates that they were to be returned; the hospitals and clinics, unlike the Red Cross, knew the identity of the hemophiliacs who had received non-heat-treated concentrates and were expected to notify them that the concentrates should be returned.

Approximately 1.7 million units of non-heat-treated factor VIII concentrate and approximately 3,200 vials of non-heat-treated factor IX concentrate were returned to the Red Cross. However, some hemophiliacs continued to use non-heat-treated concentrates after the conversion was officially completed. Some hemophiliacs were difficult to locate, and as a result were not told of the withdrawal. Some did not understand the urgency of the withdrawal because they did not know about the significantly greater safety of heat-treated concentrates. Still others were simply not told that the non-heat-treated concentrates were being formally withdrawn.

Commentary

The conversion to heat-treated factor concentrates almost completely ended the spread of AIDS among Canadian hemophiliacs. The conversion did not occur as soon as possible, as the Bureau of Biologics had directed. It was unnecessarily delayed. The conversion to heat-treated factor VIII concentrate was delayed because the Red Cross was concerned about inventory and subordinated safety in its ordering of priorities. The conversion to heat-treated factor IX concentrate was delayed because the Red Cross linked it to the conversion to heat-treated factor VIII concentrate.

No person or organization outside the Red Cross acted as an effective check on the unnecessary delays. Although some hemophiliacs who played a prominent role in the Canadian Hemophilia Society, and some physicians on its medical and scientific advisory committee, made important efforts to have the conversion take place as soon as possible, they had neither the information nor the power to bring that about. The Canadian Blood Committee, the body responsible for making policy for, and funding, the blood supply system, did nothing to minimize the delay. Indeed, in December 1984, when its executive committee considered but did not decide to write off the cost of any unused non-heat-treated factor VIII concentrate, it recognized that, if it did not do so, the Red Cross would have to "deal with" (to adopt the words of the committee's minutes) the unused inventory. Last, and most important, the Bureau of Biologics did not monitor the conversion process. It left it to the Red Cross to interpret and implement, as the Red Cross saw fit, the directive issued to it by the bureau that conversion take place "as soon as possible."

The Red Cross's implementation plan

The Red Cross, as the operator of the blood supply system, was the prime organizer of the conversion to heat-treated concentrates. It formulated the implementation plan that was proposed and debated at the consensus conference, and later executed that plan.

It is important to remember that, when the plan was formulated in the autumn of 1984, the Red Cross had, since the previous year, been facing serious problems in the supply of factor VIII concentrate because of the low yields at Connaught. The problems had periodically reached crisis proportions, and there were occasions when the Red Cross's inventory was almost exhausted. There had also been extended periods during which the Red Cross was unable to supply concentrates for elective treatment. Without an adequate supply of factor VIII concentrate, hemophiliacs were at increased risk of death or significant morbidity in the event of major bleeding or emergency surgery. The managers of the blood transfusion service were rightly concerned, and in consequence developed two views about inventory management that affected the conversion to heat-treated concentrates. First, and most important, they felt that every effort must be made to avoid wasting concentrate. Waste could result in a supply crisis that could have grave consequences for type A hemophiliacs. Second, they came to believe that a reserve inventory of factor VIII concentrate was essential to cushion the effects of unexpected supply problems and prevent them from becoming crises.

From the time that it knew that the Bureau of Biologics would require the conversion to heat-treated concentrates, the Red Cross was concerned that some non-heat-treated concentrates – already in stock or in the process of production – would be left unused and wasted. Its officials accordingly developed an implementation plan that included the exhaustion of the inventory.

For example, on 9 November 1984, after learning that the Bureau of Biologics was about to direct the conversion to heat-treated factor concentrates, Dr Davey sought, and believed that he received from Dr Boucher, the chief of the bureau's blood products division, an assurance that the directive would not prevent the Red Cross from distributing the non-heat-treated factor VIII concentrate in its inventory and in process. Dr Boucher testified that the assurance was given so that the Red Cross would know that it could continue to distribute non-heat-treated factor VIII concentrate until heat-treated concentrates were obtained, giving hemophiliacs who wanted to use the non-heat-treated concentrates continuing access to them until that time. It is clear that the Red Cross managers interpreted the assurance to mean that the Red Cross would be allowed to continue distributing the non-heat-treated concentrates until they were exhausted, for they created an implementation plan that included exhaustion of the non-heat-treated concentrates that were in inventory and in process even if heat-treated concentrates were obtained before the old stock was exhausted. On 20 November 1984, in his memorandum about the "Timing of Distribution of Heat-treated Factor VIII Concentrate," Dr Naylor related the conversion process to the time when the non-heat-treated concentrates would be exhausted rather than to the time when heat-treated concentrates would be available. Again, in his 4 December telephone conversation with Dr Card, he tied the introduction of heat-treated concentrates to the exhaustion of the inventory of non-heat-treated concentrates.

The exhaustion of the non-heat-treated inventory was linked to the accumulation of a reserve of heat-treated concentrates; the longer the introduction of the new concentrates was delayed in order to exhaust the old inventory, the greater would be the stock of the new concentrates when the transitional period ended. During May and June 1985, the conversion to heat-treated concentrates was in fact implemented in a way that minimized the remaining stock of non-heat-treated factor VIII concentrate (only one day's supply being left on 1 July) and maximized the inventory of heat-treated factor VIII concentrate (twenty-one weeks' supply being accumulated by 1 July).

On 21 November 1984, long before the May-June 1985 transitional period began, the Red Cross told Cutter not to deliver heat-treated factor VIII concentrate or, if it did deliver them, that the labelling of the concentrates should not reveal that they were heat treated. The instruction was given the day after Dr Naylor wrote his memorandum linking the timing of the conversion to the exhaustion of the non-heat-treated concentrates. It is probable that there was a fear that, if heat-treated concentrates were available and known to be available, there would be an irresistible demand for an immediate conversion that could not be met immediately. If concentrates had been obtained and the conversion process had thus begun earlier, it would have been less likely that the inventories of non-heat-treated concentrates could be exhausted.

This was not the only occasion on which the Red Cross decided not to communicate an important improvement in factor concentrates while the remaining inventory of unimproved concentrate was still to be distributed. The other occasion was in the following year, when Cutter began making commercial concentrates from plasma that had been tested for the antibody to HIV, reducing the risk of HIV contamination in concentrates. In October 1985, Cutter offered to report this improvement on the label of its commercial factor VIII concentrate that was sold under the tradename Koate. On 30 October 1985 Dr Naylor replied:

Thank you for advising us of Cutter's plan to over-label KOATE to advise users that the plasma used in its production has been screened for antibody to HTLV-III [HIV].

While the Canadian Red Cross Society Blood Transfusion Service recognizes the importance of such information, we are seriously concerned that, if labelling changes are not made in a coordinated manner, their impact on the Canadian blood system may be deleterious.

We ask, therefore, that labelling changes to advise of anti-HTLV-III screening not be introduced to product intended for the Canadian market until such time as the CRC BTS can ensure that all products will be adequately labelled. Our current estimate is that we will be in this position by July 1, 1986. We will advise you of any changes in this schedule.

At the time, Dr Naylor knew that HIV screening of plasma collected by the Red Cross had begun but would not be fully implemented until November 1985. The next shipment of plasma to Cutter was not to be made until early 1986. Because it would take at least five to six months for Cutter to deliver the factor VIII concentrate produced from that plasma, the Red Cross would not be able to convert to the exclusive distribution of screened factor VIII concentrate until 1 July 1986. Both Dr Naylor's letter and the following internal Cutter memorandum, also dated 30 October 1985, lead to the conclusion that the decision to conceal the improvement in some of the concentrate distributed by the Red Cross before July was deliberate. The Cutter memorandum reads in part:

After consulting with Derek Naylor and both Drs Martin Davey and Roger Perrault, the conclusion they have reached is that this will cause major problems for the CRC [Canadian Red Cross] in dealing with the Canadian hemophiliac community. I'm sure you can appreciate the reasons why this would be so.

Accordingly, the CRC has requested that we not sticker our KOATE product which is destined for shipment to them under our supply contract.

As they want to assure that both fractionation-contract material as well as commercial KOATE are labelled HTLV-III-screened product, it will be some months before the system is purged of non-screened product.

Inaction before the consensus conference

As the operator of the blood supply system, the Red Cross had a responsibility, independent of the regulatory requirements, to provide the least hazardous of the available factor concentrates. At the end of October 1984, the managers of the blood transfusion service concluded that "a heat-treatment procedure for factor VIII concentrate which effectively inactivates retroviruses without significantly affecting the potency of the product is now available." One would have expected them to take steps then to obtain heat-treated concentrate as quickly as possible. They did not do so. Although they withdrew an existing request for proposal for non-heat-treated factor VIII concentrate on 30 October, they did not immediately issue a new request for proposal for heat-treated concentrates. Nor did they begin a systematic survey of the availability of heat-treated concentrates or make spot purchases. Instead, they proposed that a consensus conference be held.

When, on 9 November, the managers of the blood transfusion service learned that the Bureau of Biologics was about to issue a directive that conversion to heat-treated concentrates take place as soon as possible, they took no steps to obtain those concentrates expeditiously. On 26 November, the Red Cross instructed Cutter to use glycine precipitation in processing a lot of recently shipped Red Cross plasma so that the resulting factor VIII concentrate could be heat treated, but it knew that the concentrate would not be received until April 1985 at the earliest. What was therefore required was action to obtain commercial concentrates quickly, whether by a request for proposal or spot purchases. It was not until 14 December – that is, after the consensus conference – that a request for proposal for them was in fact issued. Even then, the request called for deliveries to begin in April 1985, rather than as soon as possible. And it was not until 19 December, again after the consensus conference, that the first spot purchase was made. The concentrates from the spot purchase, in three lots, were not finished and sent to the Bureau of Biologics for testing and regulatory release until February and March 1985; only after regulatory release had occurred could they be shipped to the Red Cross, in the last days of April 1985.

It is impossible to know with precision how much earlier conversion to heat-treated factor VIII concentrate could have occurred if the Red Cross had acted in November or early December 1984 to obtain commercial heat-treated concentrates. In a memorandum dated 19 November, Dr Naylor said that a request for proposal issued at that time would result in deliveries of heat-treated factor VIII concentrate at the end of February 1985. The evidence about the availability of concentrates from the U.S. manufacturers described earlier justifies the conclusion that, if they had been ordered earlier, heat-treated

factor VIII concentrate could have been obtained before April 1985. Inaction in November and early December 1984 led to a delay in the conversion to heat-treated factor VIII concentrate.

Dr Davey testified that the Red Cross could not convert to heat-treated factor VIII concentrate until it had the Canadian Blood Committee's permission – first, because the price of heat-treated concentrate was higher than the price of non-heat-treated concentrate, a difference in the range of 19 to 25 per cent; and second, because it would hurt the interests of Connaught. From the inception of the committee, there had been acrimony between it and the Red Cross whenever the Red Cross spent substantial funds for new purposes without the prior approval of the committee. From the mid-1970s, there had been friction with Ontario whenever the Red Cross did anything that hurt Connaught's interests. The result was that the Red Cross had learned not to take actions that would significantly increase cost or that would have a negative impact on Connaught's interests without the prior approval of the committee. Dr Davey's explanation reflects the historical relationship between the Red Cross and the Canadian Blood Committee, but it does not justify the slowness of the Red Cross to obtain heat-treated factor concentrates, particularly after the Bureau of Biologics issued its directive to the Red Cross. That the Red Cross felt that it needed the approval of the Canadian Blood Committee before it could act on its own conclusions and follow the directive of the bureau demonstrates a fundamental dysfunction of the blood system.

The monitoring of the conversion process

The Bureau of Biologics's directive to the Red Cross and the manufacturers was a demand that the fractionators and the Red Cross supply safer products. In order to determine whether the Red Cross was implementing the conversion "as soon as possible," the bureau needed to know the amounts of non-heat-treated and heat-treated concentrates the Red Cross held throughout November 1984 to July 1985. It did not obtain that information. In short, the bureau did nothing to ensure that its directive was followed. The Red Cross was left to define the meaning of "as soon as possible."

The consensus conference

The Red Cross presented its plan for conversion to heat-treated concentrate at the consensus conference held on 10 December 1984. That plan included the proposal that the inventory of non-heat-treated factor VIII concentrate be exhausted during the conversion process, even if heat-treated concentrates were obtained before the old stock was exhausted. It may be that not all the participants at the conference understood what was being proposed as they listened to the presentations. Some of those who listened did understand, however, and they initiated the discussion that ensued. The acceptability of the proposal was debated with such vigour that no one present could then have failed to understand what was being proposed.

Dr Card, making the official presentation on behalf of the Canadian Hemophilia Society, asked that the conversion to heat-treated concentrates take place as soon as possible, but he did not oppose the Red Cross's proposal to exhaust the supplies of non-heat-treated factor VIII during the conversion process. However, another representative of the society did oppose it. Mr Poyser, the society's representative on the Canadian Blood Committee's advisory subcommittee, was one of the strongest critics of the proposal. He was joined in that criticism by three other members of the advisory subcommittee, Dr Inwood, Dr Koopmann, and Dr McElligott, each representing a national medical institution.

The Red Cross's proposal, because it contemplated exhausting the inventory of non-heat-treated concentrates no matter when heat-treated concentrates were obtained, was incompatible with the directive of the Bureau of Biologics that the conversion to heat-treated concentrates take place "as soon as possible." Despite that incompatibility, the bureau's representatives at the conference did not then or later express any opposition to the proposal. Moreover, the proposal and the vigorous discussion that followed did not prompt the bureau to recognize the need to monitor the conversion process to ensure compliance with its directive.

The members of the Canadian Blood Committee who attended the consensus conference acted as observers and did not participate actively in the proceedings. The recommendations of the conference were considered at the meeting of the committee's executive committee the next day. When, during that meeting, the executive committee was asked whether the cost of unused non-heat-treated concentrate would be written off, it gave no answer. The question put to the executive committee gave it the opportunity to decide the most contentious issue left open at the end of the conference – whether the inventory of non-heat-treated factor VIII concentrate should be exhausted during the conversion process. It did not resolve the issue. The executive committee should have said that the cost of any unused non-heat-treated concentrates would be written off and should have expressly directed that the distribution of non-heat-treated concentrates should be discontinued as soon as possible, regardless of the stock of non-heat-treated concentrates that would be left unused. That the Red Cross was not told that there would be a writeoff, and was left until December 1985 to wonder whether there would be a writeoff, is another example of a fundamental dysfunction of the blood system.

Communications by the Red Cross in advance of conversion

During October to December 1984, the Red Cross's public statements underestimated the risk of HIV infection from the use of factor concentrates. Moreover, those statements did not reveal the opinion of the managers of the blood transfusion service – that the risk of HIV infection would be diminished if heat-treated concentrates were used.

In October 1984, the managers of the blood transfusion service had little reason to doubt that AIDS could result from the use of factor concentrates and that heat treatment was effective in inactivating HIV in factor concentrates. They did not say so in an article they wrote which was submitted to and published by *Hemophilia Today*. In December 1984, in the press release issued by the Red Cross and the Canadian Hemophilia Society after the consensus conference, the language used understated the risk of HIV infection from the use of non-heat-treated concentrates that was known to the managers of the blood transfusion service. A reader would reasonably have inferred from these communications that the conversion to heat-treated concentrates was far from urgent. This, in part, may explain why some hemophiliacs continued to use non-heat-treated concentrates after they were recalled at the beginning of July 1985.

Communications during the transitional period

There was no agreement at the consensus conference that there must be a transitional period. There was agreement only that there would be a transitional period, during which both non-heat-treated and heat-treated concentrates would be distributed, if at some time the supply of heat-treated factor VIII concentrate was insufficient to treat all persons with type A hemophilia. The Red Cross's interpretation, as expressed by Dr Perrault the next day to the executive committee of the Canadian Blood Committee, was that the transitional period was to begin no later than 1 May. It was to end as soon as possible, but no later than eight weeks after it began. In essence, the transitional period, if one was necessary, was to begin as soon as possible and to end as soon as possible.

Information about the amount of heat-treated concentrate in stock during the transitional period was essential because it was that amount that determined when it was possible to end the transitional period. During the transitional period, the national office of the blood transfusion service did not reveal its inventory levels to the Canadian Hemophilia Society and its medical and scientific advisory committee, or to its own medical directors.

Hemophiliacs, the physicians treating them, and the local medical directors were unaware of the national inventories of heat-treated factor VIII concentrate throughout the transitional period. The Canadian Hemophilia Society and its medical and scientific advisory committee were also unaware. This lack of information explains why there was no objection when the Red Cross continued to distribute non-heat-treated concentrates until 1 July while it was accumulating a large inventory of heat-treated factor VIII concentrate.

The transition to heat-treated factor VIII concentrate

On 26 November 1984, the Red Cross told Connaught that it had decided to accept delivery of its non-heat-treated factor VIII concentrate until the end of March. Because this concentrate was already in process, the plasma

being used to produce it could not be redirected to Cutter to produce heat-treated concentrate. The Red Cross also decided to accept delivery of non-heat-treated factor VIII concentrate that was already in process at Cutter; it was too late to heat treat these lots of concentrate. The Red Cross also decided to make a spot purchase of non-heat-treated factor VIII concentrate from Cutter in November 1984. These were reasonable decisions, but only if the purpose of processing and purchasing the non-heat-treated concentrates was to provide a reserve inventory against the chance that sufficient heat-treated concentrates could not be obtained later; in other words, it was reasonable to take delivery of these concentrates only if it was planned not to use them once sufficient heat-treated concentrates were received.

On 15 May, the Bureau of Biologics approved the distribution of the lot of heat-treated factor VIII concentrate that contained plasma that was implicated in the transmission of hepatitis. When that decision was made, the Red Cross already had nine weeks' supply of heat-treated factor VIII concentrate in stock, all of which could have been distributed. This was a substantial inventory. The Red Cross had managed with significantly lower inventories of factor VIII concentrate from time to time during 1983 and 1984. The transitional period for factor VIII concentrate should have ended on 15 May. On that date, the Red Cross should have stopped distributing non-heat-treated factor VIII concentrate, holding the remaining three to four weeks' supply in reserve for unforeseen emergencies. Instead, the transitional period – and the continued distribution by the centres of non-heat-treated concentrates – continued beyond 5 June, when the Red Cross held seventeen to eighteen weeks' supply of heat-treated factor VIII concentrate, and beyond 13 June, when it had twenty-two weeks' supply of heat-treated factor VIII concentrate, until 1 July. Because the transitional period did not end on 15 May, there was further delay beyond that caused by the inaction in late 1984.

The extension of the transitional period to the end of June 1985 allowed the Red Cross to accumulate between five and six months' supply of heat-treated concentrate. After 1 July, when the unused non-heat-treated concentrates were withdrawn, only two weeks' supply of non-heat-treated factor VIII concentrate was returned to the Red Cross by hospitals and hemophiliacs. Even if the Red Cross had immediately distributed two months' supply of heat-treated factor VIII concentrate on 1 July to restock hospital inventories and the home supplies of hemophiliacs, it would have had a reserve of three months' supply or more. At a time when hemophiliacs were being exposed to the risk of HIV infection through the use of non-heat-treated concentrates, safety concerns should have been given priority over those of reserves.

The transition to heat-treated factor IX concentrate

The Red Cross's memorandum of the meeting between the Red Cross and Cutter on 4 December and the presentations by Dr Davey and Dr Naylor at the consensus conference demonstrate that the Red Cross planned to

introduce heat-treated factor VIII and factor IX concentrates at the same time, even if the factor IX concentrate was available before the factor VIII concentrate.

Although type A and type B hemophilia both result from deficiencies in the coagulation system, they are different conditions and are treated with different products. The introduction of heat-treated factor IX concentrate for use by persons with type B hemophilia was unacceptably linked to the introduction of heat-treated factor VIII concentrate for use by persons with type A hemophilia.

The delay in introducing heat-treated factor IX concentrate was incompatible with the directive from the Bureau of Biologics that heat-treated concentrates be introduced as soon as possible. No one from the bureau, however, expressed opposition to the proposed delay.

Despite the fact that 10,000 vials of custom-fractionated factor IX concentrate had been heat treated for the Red Cross by 4 December 1984, they were not obtained and distributed as quickly as possible. It was not until late March 1985, three months after the concentrates had been manufactured, when it became apparent that the approval of labelling by the regulators would not occur in time to meet the start of the transitional period, that action was taken to obtain them as quickly as possible. As it turned out, because of the prolonged and unforeseen labelling problem, heat-treated factor IX concentrate was introduced even later than heat-treated factor VIII concentrate.

It is difficult to understand why, when the labelling problem became apparent, the Red Cross did not seek to import the concentrates with U.S. labelling. The bureau allowed U.S. labelling for heat-treated factor VIII concentrate. Had such a solution been applied to the 10,000 vials of custom-fractionated heat-treated factor IX concentrate prepared in December 1984, the first delivery could have been made as soon as licensing occurred on 10 April 1985 – that is, approximately fifty days earlier than it did.

Moreover, after 30 May, when there was eight weeks' supply in hand, only heat-treated factor IX concentrate should have been distributed. Additional supplies were expected in early July. The eight weeks' supply was not only sufficient to meet the usual demand but also afforded three weeks' reserve inventory for unforeseen emergencies.

The consequences of delay

In 1984, Dr Christos Tsoukas, an immunologist practising in Montreal, and later a member of the division of clinical immunology and the director of the immune deficiency treatment centre at the Montreal General Hospital and an associate professor of medicine and an associate director of the AIDS centre at McGill University, began a study of AIDS among 372 persons with coagulation disorders being treated at eleven centres in nine provinces. These persons represented approximately one-sixth of the persons with coagulation

disorders in Canada. Of the total, 174 persons (nearly 50 per cent) tested HIV positive in 1984 at the beginning of the study. Fourteen more persons tested HIV positive before 1 July 1985, and five more persons tested HIV positive between July 1985 and May 1986. The dates on which the persons first tested positive were not the dates on which they were infected. The blood samples analysed in the study were taken approximately every six months; and there was a period after infection during which the antibody to HIV was not detectable. As a result, the first HIV-positive test result for a person could occur considerably more than six months after infection.

Dr Tsoukas presented the results of his study at a conference in February 1988. At that time, he said that all but one of the five persons who first tested HIV positive between July 1985 and May 1986 appeared to have been infected through the use of non-heat-treated concentrates. At the hearings, he testified that the five persons must have been infected at approximately the time of the conversion to heat-treated concentrates, and he recognized the possibility that three of them might have been infected during May and June 1985 – that is, during the transitional period.

Although very many hemophiliacs had been infected with HIV before 16 November 1984, the day on which the Bureau of Biologics issued its directives that required that the conversion to heat-treated concentrates take place as soon as possible, some, who later were infected, had not yet been infected. On all of the evidence – including the risks inherent in the custom-fractionated non-heat-treated concentrates (reviewed in Chapter 14), the study showing the continuing infection of hemophiliacs in the United States through the use of commercial non-heat-treated concentrates (also reviewed in Chapter 14), and Dr Tsoukas's study – it is impossible to avoid the conclusion that, if heat-treated concentrates had been introduced as soon as possible, some of the hemophiliacs who were infected would have avoided infection.

Safety in Heat-Treated Concentrates

By late 1985, a number of safeguards had been instituted to protect Canadian hemophiliacs from the risk of acquiring HIV from factor concentrates. In particular, all coagulation blood products distributed after 1 July 1985 in Canada were heat treated to inactivate HIV, and HIV testing of blood and plasma donations had become almost universal by the spring of that year in the United States and by early November in Canada. There was justification for a renewed sense of confidence among Canadian hemophiliacs. A little more than two years later, that confidence was badly shaken.

A multicentre study of the immunological status of Canadian hemophiliacs, coordinated by Dr Christos Tsoukas in Montreal, had begun in late 1984. It had not been designed for the purpose of surveillance. In the autumn of 1987, however, this routine monitoring of a broad section of Canadian hemophiliacs detected a cluster of patients who had abruptly become HIV-antibody positive. All had used heat-treated products exclusively.

Dr Tsoukas alerted the physicians treating patients with hemophilia; the Canadian Red Cross Society (Red Cross) and the federal regulatory bureau, the Bureau of Biologics, were informed; and product replacements were begun. Eventually the source of infection was traced to one product – H.T. Factorate, manufactured by the Armour Pharmaceutical Company – and, in particular, to the heat-treatment process Armour then used to virally inactivate the concentrates it sold to the Red Cross. The ensuing publicity shattered Canadian hemophiliacs' recently renewed and still fragile confidence in the safety of their therapeutic regimens. More than any other single event, it galvanized the survivors of contaminated coagulation preparations and their physicians to demand safer plasma products and an active role in the reformation of the Canadian blood system. It was, in the words of Dr Kaiser Ali, then the chair of the medical and scientific advisory committee of the Canadian Hemophilia Society, a "telling point in the history of hemophilia care nationally in Canada."

Heat-treated blood products in the Canadian market

The Armour Pharmaceutical Company (Armour) was one of several U.S. manufacturers that supplied the Red Cross with fractionated blood products. Armour's Canadian affiliate during the early 1980s operated under the name of USV Canada Inc. By 1986 it had merged with Rorer Canada Inc. and was operating under the Rorer name. Armour is today owned by the French company Rhône-Poulenc Rorer Inc.

The Red Cross began distributing factor concentrates in the late 1970s. Armour did not make its first formal proposal to supply factor VIII concentrate to the Red Cross until late 1983. It was then awarded a contract to supply ten million units of Factorate (Armour's tradename for its intermediate purity factor VIII product) during 1984, conditional upon the licensing of the product by the Bureau of Biologics. The bureau licensed Factorate on 17 January 1984.

In October 1984, the Red Cross asked USV Canada and other suppliers to submit a proposal to supply non-heat-treated antihemophilic factor concentrate for the following year. At the end of the month, however, the Red Cross informed all potential fractionators, including Armour, that the request was withdrawn. This was done in anticipation of a conversion to a heat-treated product. All the fractionators were further informed that a new request would be issued in January 1985.

Heat-treated antihemophilic factor concentrates were not commercially available until the 1980s. Their development had begun during the late 1970s, when some manufacturers of factor concentrates were seeking ways to inactivate viral agents – at first, those causing hepatitis – transmitted by their products. A German manufacturer, Behringwerke AG, was the first to claim success; its "heat sterilized" factor VIII was licensed in Germany in May 1981. The first U.S. licence for heat-treated factor VIII concentrate was granted to the Hyland Therapeutics Division of Travenol Laboratories Inc. (Hyland) in March 1983 for its Hemofil-T; that product, during processing, was heat treated at 60°C for seventy-two hours. Eight months later, in November 1983, Hemofil-T, manufactured by Hyland (later part of the Baxter Healthcare Corporation), became the first heat-treated factor concentrate to be approved for use in Canada. A year later, in November 1984, the Bureau of Biologics licensed another U.S. manufacturer, the Cutter Biological Division of Miles Laboratories Inc. (Cutter), for its Koate HT; this was approximately ten months after the product was licensed in the United States. The viral inactivation process used by Cutter (currently part of Bayer Inc.) involved heating at 68°C for seventy-two hours.

Armour had also entered this field. On 25 January 1984, it received an amendment to its U.S. product licence for an optional heat-treatment process

of 60°C for thirty hours in the production of antihemophilic factor concentrate. Its heat-treated products had the tradenames H.T. Factorate (an intermediate purity preparation containing twenty to thirty times as much factor VIII, after it was reconstituted by adding sterile water, as an equal volume of plasma) and H.T. Factorate Generation II (a more highly purified preparation that contained, upon reconstitution, twenty-five to forty times as much factor VIII as an equal volume of plasma). Armour's claims for these products at the time referred to reducing the risk of the transmission of viral hepatitis. The first lots of H.T. Factorate were available for distribution in the United States in February 1984. Eight months later, on 30 October 1984, USV Canada, on behalf of Armour, applied to the Bureau of Biologics for a licence for H.T. Factorate in Canada.

The U.S. government announced the discovery of the causative agent of AIDS (then identified as the retrovirus HTLV-III and now called the human immunodeficiency virus, HIV) in April 1984. By that time, all four U.S. fractionators (Armour, Cutter, Hyland, and the Alpha Therapeutic Corporation) had licences for heat-treated factor VIII concentrate, and investigations soon began into the effectiveness of their heat-treatment processes on HIV. Preliminary research revealed that HIV, which is a retrovirus, was susceptible to heat. In a report published in September 1984, Dr Jay A. Levy and colleagues concluded that "[p]rolonged heating at 68°C inactivates retroviruses, and adoption of this procedure in the manufacture of factor VIII concentrates should result in materials free of these infectious viruses."

In October 1984 Meloy Laboratories Inc. (Meloy), an affiliate of Armour, was awarded a contract by a U.S. biotechnology group to prepare large quantities of the LAV virus (another name given to HIV) for research purposes. At Armour's initiative, Meloy soon began experiments to assess the effect of heating on the virus, using Armour preparations "spiked" with HIV – that is, preparations to which HIV had been added. In November, Armour learned that the U.S. Food and Drug Administration (the regulator of blood products) and the U.S. Centers for Disease Control in Atlanta were collaborating in studies to examine the effects on HIV infectivity of heating antihemophilic factor concentrate in liquid and dry form. Dr J.S. McDougal of the Centers for Disease Control had developed an assay method to measure viral activity which was capable of detecting HIV at levels as low as ten living viruses per millilitre of blood. In these "McDougal studies," commercial factor VIII and factor IX concentrates were spiked with HIV and then exposed to heat at the temperatures and for the lengths of time specified by their manufacturers. Armour factor concentrates were not among the commercial products tested. Armour officials believed that it would be "wiser to conduct the [spiking] experiments in house with LAV [HIV] under our own control than to begin contracting the work on the outside."

Armour asked for a copy of Dr McDougal's preliminary findings and received it from Dr Bruce Evatt in a letter dated 29 November 1984. Dr Evatt

was then the director of the division of host factors in the Center for Infectious Diseases at the U.S. Centers for Disease Control. Dr Evatt reported that no viable viruses were detected following various heat-treatment procedures. He concluded that “[b]ecause LAV [HIV] appeared to be extremely heat labile [i.e., sensitive to change], we believe that the procedures presently used by manufacturers for heat treatment of hepatitis virus would adequately inactivate LAV virus.”

In Canada, roughly two weeks earlier, on 16 November, the Bureau of Biologics had issued directives to the Red Cross and the manufacturers of factor concentrates recommending that non-heat-treated factor concentrates be replaced with heat-treated concentrates as soon as possible. On 14 December, the Red Cross asked all fractionators to submit a proposal to supply heat-treated antihemophilic factor for the period April 1985 to March 1986. Armour’s proposal, forwarded to the Red Cross in early January, included a copy of Dr Evatt’s letter and an Armour-prepared table summarizing the results of the McDougal experiments. On 19 February 1985, the Red Cross awarded Armour a contract to supply ten million heat-treated units of factor VIII concentrate, conditional upon it being licensed by the Bureau of Biologics. By 1 May 1985, the date the first vials of heat-treated factor concentrate were distributed in Canada, Armour had supplied a total of approximately 5.2 million units of H.T. Factorate to the Red Cross, more than half of Armour’s contractual obligation for the entire year. Until mid-1985, Canadian hemophiliacs had been treated with non-heat-treated factor concentrates. (A detailed description of the decision to convert to heat-treated concentrates and of the conversion process is given in Chapter 15.)

In their reviews for the Bureau of Biologics of Armour’s submission for a licence for H.T. Factorate, both Dr J.E. Synek, the head of the plasma derivatives section of the bureau’s blood products division, and Dr Wark Boucher, the chief of that division, had noted that Armour’s method of viral inactivation (sometimes referred to as a “short-heat” process) involved heating at a lower temperature and for a shorter period than the processes used by some competitors. (Cutter’s preparation, for example, which had been licensed in Canada in November 1984, was heat treated at 68°C for seventy-two hours.) In recommending approval of Armour’s submission on 26 March 1985, however, Dr Boucher had stated that “[t]he Armour heat treatment procedure has been shown to inactivate at least 6.0₁₀ logs of the human retrovirus, LAV [HIV]” – that is, the procedure reduced the concentration of HIV a million-fold. He had concluded that “[t]he procedure therefore meets the requirements for heat inactivation.” The Bureau of Biologics’s licensing of H.T. Factorate followed on 12 April 1985. The federal government has been unable to locate any documents that support the bureau’s evaluation of Armour’s short-heat process. Dr Boucher was unable to recall the documents upon which he had relied in reviewing Armour’s submissions.

Concerns about the effectiveness of heat treatment

As of early 1985, there were few publicly expressed doubts about the safety of the methods used by different fractionators to inactivate HIV. Within Armour, however, there were two reasons for increased corporate concern about the effectiveness of the company's short-heat process. The first derived from confidential reports of viral inactivation studies conducted for Armour itself. The second came from a growing number of international reports that linked positive tests for HIV antibody to the use of Armour's H.T. Factorate. Some of these reports became public knowledge in 1986. In contrast, most of Armour's internal or commissioned viral inactivation studies were never made public until they were filed as exhibits during the Inquiry. Far more important, Armour never disclosed the results of these studies to the Bureau of Biologics or the Red Cross. An account of these events follows.

Articles about the efficacy of heat treatment began to appear in peer-reviewed journals in the summer of 1985. In June, *The Lancet* reported the results of further experiments by Dr Levy and his colleagues. They concluded that retroviruses could withstand procedures used to purify factor VIII concentrate; however, heating lyophilized (freeze-dried) factor VIII concentrate for seventy-two hours at 68°C or the liquid product for ten hours at 60°C would eliminate infectious HIV if it was not present in the original plasma at more than one million infectious particles per millilitre. Two months later, the *Journal of Clinical Investigation* published a report of the McDougal thermal inactivation studies at the Centers for Disease Control. These McDougal studies indicated that heat treatment at 60°C for twenty hours (that is, ten fewer hours than those in Armour's dry short-heat process) "should provide a large, if not absolute, margin of safety." Dr McDougal's data showed no detectable virus in lyophilized factor products after heating at either 68°C or 60°C. He and his colleagues did note, however, that "the relationship between the lower limits of sensitivity for infectious virus in this assay and infectivity in man is unknown" and, as Armour explained in its submissions, the methodology was such that McDougal's assay actually "could not test whether virus was present at less than 2 logs" (that is, could not detect fewer than 100 viruses per millilitre). Relying primarily on these studies, Dr McDougal and Dr Evatt of the Centers for Disease Control and Dr John Petricciani, director of the division of blood and blood products of the U.S. Food and Drug Administration's Office of Biologics Research and Review, calculated the maximum concentration of HIV likely to be present in commercial antihemophilic factor concentrate before heat treatment to inactivate the virus. In a letter published in *The Lancet* of 19 October 1985, they concluded:

There still seems to be enough of a safety factor afforded by AHF [antihemophilic factor] heat treatment to permit the conclusion that infectious LAV/HTLV-III [HIV] is unlikely to be present in currently licensed

heat-treated AHF, and that the use of such products should not result in additional cases of AIDS in persons with hemophilia.

Armour was conducting its own studies. From January to August 1985, Dr Alfred Prince, a virologist with the New York Blood Center, conducted a series of studies on behalf of Armour affiliates to determine the effect of Armour's heat-treatment process on HIV infectivity in its coagulation products. The studies were performed on three Armour products: intermediate purity factor VIII concentrate (H.T. Factorate "Generation I" or "Gen. I"), the only Armour factor VIII product licensed and sold in Canada; high purity factor VIII concentrate (H.T. Factorate "Generation II" or "Gen. II"); and a factor IX concentrate, manufactured under the tradename "Prothar," which, in its heat-treated version, was never licensed in the United States or Canada. The experiment in each case involved spiking samples of the Armour concentrates by adding known amounts of laboratory-grown HIV, freeze drying and heating the spiked concentrates, and then calculating the reduction in the amount of added HIV.

The results of the first study, conducted on Generation I and II factor concentrates, were submitted to Armour's officials on 24 January 1985. The concentration of HIV (the titre) used in the spiking was relatively low and, as a result, "[t]he most that can be concluded from the study is that the combined effect of lyophilization and heating inactivated ≥ 2.5 – 3.0 logs" (that is, reduced the concentration of the virus to between one three-hundredth and one one-thousandth of the original). This result was disappointing because, as Dr Prince wrote in his reporting letter, "we were unable to show a [greater than] 5 log kill as had been hoped." A five-log reduction in viral concentration was then widely considered an appropriate, if arbitrary, standard within the industry. Accordingly, a second series of tests at "higher challenge levels" was undertaken.

The results of the second Prince study, involving only Generation II and factor IX concentrates, suggested "a total process efficacy of about 4 Log_{10} ," or a reduction by a factor of 10,000. A companion study was conducted exclusively on H.T. Factorate Generation I, distribution of which was to begin in Canada the next month. The findings were submitted to Armour on 5 April 1985, a week before H.T. Factorate was licensed by the Bureau of Biologics. Dr Prince reported that lyophilization alone caused a one-log reduction in titre, and concluded that, when combined with heating, "[t]he results suggest a total process efficacy for inactivation of HTLV-III [HIV] in Gen. I under the conditions used of about 3.0 Log_{10} " (that is, a reduction to one one-thousandth of the original concentration). Although no one then knew the critical infectious dose of HIV, the industry standard for viral attenuation was a five-log reduction, meaning that a viral load as high as 100,000 virus particles per millilitre could be effectively eliminated. The results of Dr Prince's second study demonstrated that the heat-treatment process used by Armour

(including lyophilization) reduced the viral load by two logs (or one hundred times) less than the industry standard. At the time, the Bureau of Biologics considered a six-log (million-fold) reduction as the accepted safety standard within the field of virology.

Third and fourth studies conducted in May and June 1985 were aborted because of equipment failures. Dr Prince completed his fifth and apparently final viral inactivation study for Armour on 5 August 1985. Its purpose was to evaluate the effect of dry heating at 60°C on Generation II and factor IX products. Dr Prince told Armour that the results of his final study "reveal that even the 30 hour heated samples still contained infectious virus."

Dr Prince's results were inconsistent with those of other studies then available to Armour. Dr McDougal had not detected virus in his spiking experiments, nor had Litton Bionetics Inc. (Litton) in other tests directed by Armour of its heat-treated and non-heat-treated lyophilized antihemophilic factor products. Litton used samples manufactured from a plasma pool containing material from a person who had developed AIDS. The results, reported to Armour on 28 August 1985, did "not indicate the presence of HTLV-III [HIV] virus in the samples submitted for virus isolation." Unfortunately, the degree of viral contamination of the plasma pool from which the samples were drawn is unknown, as, it appears, is the viral detection limit of Litton's test procedure. The Litton study did not assist in determining the efficacy of Armour's short-heat process because no infectivity was detected in either the heat-treated or the non-heat-treated sample.

Armour also retained Dr McDougal to conduct infectivity studies using its products. Samples were sent to him in June, August, and the early autumn of 1985. The first two sets of samples were spiked with very low titres of HIV provided by the Centers for Disease Control. No detectable virus was discovered after lyophilization and heating, using the same type of assay as used in Dr McDougal's earlier study. A third set of samples was spiked with higher titre prepared at Meloy. The results of this experiment, if any, are not available. An internal Armour memorandum dated 18 October 1985 records Dr McDougal as "absolutely agree[ing] that the type of assay performed by Dr Prince is more sensitive for the detection of small numbers of viruses" than his own standard assay, and that he had developed "a more sensitive assay, very similar to the Prince assay" that he was about to use in his experiments. Armour encouraged Dr McDougal to repeat his earlier spiking studies of commercial antihemophilic factor products using the more sensitive assay, but the results of such tests, if any, were never reported to Armour or to Meloy.

Without an industry-wide standardized assay, Armour was concerned that publication of the Prince studies would place it at a competitive disadvantage. When Dr Prince proposed publication of his data, Armour told him that it considered his experiments to be of great importance, but expressed concern for "the potential substantial negative commercial impact of a

publication or presentation indicating that infectious virus was still present in [Armour] products without simultaneously addressing the results obtained with the McDougal assay ... that has become more or less the standard for the industry." It recommended that Dr Prince delay publication until directly comparable McDougal data were available. This information, according to Armour, was never received. However, Dr McDougal did inform Armour in mid-October 1985 that he was "unaware of any data that can predict the minimal number of infectious particles required to trigger clinical disease in man." This response left unanswered the question whether the amount of residual virus detected in Dr Prince's experiments was capable of transmitting AIDS.

In late October or early November 1985, Dr Prince submitted to Armour a manuscript that he proposed to publish, summarizing his experiments. He did not identify the manufacturer by name in the manuscript, but reported that, based on his data and calculations, the lyophilization and heating of "commercial preparations" at 60°C for thirty hours resulted in "little or no inactivation." He added that, "[t]he low purity F[actor] VIII preparation seemed to provide exceptional stabilization with little or no inactivation being seen up to 48 hours of heating and only 2.0 Log₁₀ inactivation seen in 2 samples heated for 72 hours." He concluded:

These findings indicate that in the present study pasteurization at 60°C in the dry state had only a modest process efficacy for inactivation of HTLV-III/LAV [HIV]. Lyophilization itself inactivates 0.5–2.0 Log₁₀ of infectivity, however as lyophilized products transmit AIDS, this is clearly not sufficient to yield sterile products.

Dr Prince acknowledged in his manuscript that his laboratory's findings were "in marked contrast" to the McDougal data:

It is difficult to explain the difference between the results reported by McDougal et al and the present findings. These differences may reflect the use of antigen assays by McDougal et al for detection of infected cultures instead of reverse transcriptase assays which were used in this study. Heated virus may infect more slowly and thus be less detectable by antigen assays at the times when cultures were harvested. Furthermore the use of macro cultures may have permitted the detection of small quantities of residual virus in the present study. An additional important variable is the moisture content of the samples ... The moisture content of the samples tested by McDougal was not specified.

Many years later, in a 1996 letter published in *Nature*, Dr Prince said that his work for Armour "showed [McDougal's] report to be methodologically flawed."

In his manuscript, Dr Prince noted that dry heat treatment had "been shown to have only modest sterilization effect on Hepatitis B virus," but stressed that his findings "do not necessarily indicate that presently available dry heat treated products are unsafe with respect to transmission of AIDS." Some of these dry heat-treated products, he pointed out, "are heated at higher temperatures than the 60°C which we evaluated."

Armour refused to give Dr Prince permission to publish his manuscript. Dr William Terry, then president of Meloy and a member of Armour's plasma executive committee, summarized Armour's reasons in an internal memorandum dated 8 November 1985:

The data in this [Dr Prince's] manuscript indicate that Generation I, Generation II and factor IX are not rendered virus-free when they have been contaminated with HTLV-III [HIV] and heated in the dry state at 60°C for even as much as 72 hours. I told Dr Prince that while our foremost concern was the safety of patients receiving these products, these data taken in isolation could only be confusing to the scientific community, the treatment community and the public and that we therefore were not prepared to give him permission to publish.

Despite Armour's refusal, Dr Prince's findings were published in *The Lancet* some seven months later, in May 1986, after he reproduced them in independent studies at the New York Blood Center. Parts of *The Lancet* report were identical in language to his suppressed manuscript. Dr Prince did not identify Armour, but noted that his experiments involved heating "commercial preparations" produced at the New York Blood Center for different periods of time at 60°C. "The virus inactivation resulting from heating alone was surprisingly modest," he reported, varying between zero and one log at ten hours and between two and four logs after seventy-two hours of heating. He noted that two cases of HIV seroconversion (that is, of hemophiliac patients who had changed from testing negative to testing positive for HIV antibody) had recently been reported in recipients of heat-treated factor VIII concentrate of an unidentified manufacturer, and observed that his "finding of only modest sterilization process efficacy for HIV adds to concern about the efficacy of this procedure." Dr Prince acknowledged that "some products are heated above 60°C." "Nevertheless," he concluded that "these findings indicate the need for caution in relying on the efficacy of dry-heat sterilization." A year later, in a review of developments in virus-free blood derivatives published in the *European Journal of Epidemiology*, he repeated the need for caution, noting that heating in the lyophilized state "inactivated only modest amounts of HIV in tissue culture studies of the 60°C process."

Armour's "recombinant DNA steering committee" reviewed the Prince studies at a meeting on 15 October 1985, well before publication of their explication in *The Lancet*. Minutes of that meeting record that the members

of the committee decided it would be "unwise" to inform the U.S. Food and Drug Administration of what they called "preliminary results" until additional viral inactivation studies had been carried out internally at Meloy to establish that the Armour heat-treatment method met the viral inactivation claims of its competitors. Without these data, Armour feared that it was in danger of losing a large part of its share of the market, such as the 1986 contract for Canada and another for France. In the words of one senior Armour officer, "[t]he issue is not one of regulation, but rather marketing." Armour officers assumed that the standard used by their competitors to detect virus was less stringent than that used by Dr Prince. They discussed using the less sensitive assay standard used by their competitors and the feasibility of modifying Armour's heat-treatment method. One officer urged moving immediately to heat treating at higher temperatures for longer periods to improve the safety of Armour's product, but others argued that such a course of action would take too long to effect and would be very expensive. The committee decided to continue distribution of concentrate heat treated at 60°C for thirty hours, while simultaneously studying the efficacy of that process.

Armour's additional studies tended to confirm Dr Prince's findings. Internal viral inactivation studies were conducted at Meloy from October to December 1985 and other studies were carried out in 1986, exploring the comparative efficacy of heating at various temperatures and times. From these experiments, as reported in an internal memorandum, it was "apparent that heating at 60°C for either 30 hours or 60 hours leaves substantial residual infectious virus" and that "heating at 68°C for 72 hours appears much more effective in reducing infectivity." The Meloy "Monthly Summary for June" 1986 noted that "the basic conclusions from existing data are inescapable. There is a significantly greater viral reduction at 68/72 hrs."

Armour retained a scientist at the Paul Ehrlich Institute in Germany to conduct a further external viral inactivation study. The report was promising – the short-heat process "led to complete inactivation" and no residual infectiousness of any kind was detectable – but Armour's internal review of the report judged the conclusions overstated. Dr Terry, Meloy's senior scientist, reviewed the study in May 1986 and reported that the procedures were faulty, the conclusions invalid, the report misleading, and the results unproven.

The results of the Prince studies were not transmitted to the regulatory bodies with which Armour dealt. The governing Canadian legislation required disclosure of such information. Section C.04.010(b) of the *Food and Drug Regulations* provided: "Every [licensed] manufacturer shall notify the Minister immediately of any deficiency or alleged deficiency concerning the quality, safety, or efficacy of any drug manufactured by him." The Bureau of Biologics was never informed by Armour of the results of any of its studies of the efficacy of its short-heat process. The Prince studies were not seen by the bureau until access was provided through this Inquiry in the autumn of 1995. The Government of Canada's position in its submissions is that because Armour

did not notify the Minister of the results of Dr Prince's study, it "failed to comply with the *Food and Drug Regulations*." Dr Boucher testified that he believed that knowledge of the Prince studies, along with all other relevant data, "would have made a difference in the final decision" taken by the Bureau of Biologics to license H.T. Factorate manufactured using the short-heat process. The bureau would have been even more cautious, he said, had it known that Armour's product was not among the commercial heat-treated preparations reviewed by the Centers for Disease Control in the McDougal study.

The regulatory affairs officer for Armour's Canadian agent, USV Canada, was never informed of any reports by Dr Prince, Meloy Laboratories, or the Paul Ehrlich Institute before she left the company's employ in the fall of 1986. Had she become aware of studies or reports touching on the efficacy or safety of Armour's viral inactivation process, she stated, she would have conveyed this information immediately to the Bureau of Biologics. The Red Cross, which distributed many millions of units of H.T. Factorate from 1985 to 1987, was not given information about the Prince, Meloy, or Paul Ehrlich Institute studies at the time, and did not receive copies of them until the hearings in October 1995.

Concerns about reported cases of seroconversion

The second source of Armour's internal concern developed during the second half of 1985, when it learned that five hemophiliacs who had used H.T. Factorate had seroconverted. The first two cases were reported on 10 July to Armour officials in the United Kingdom. On 6 September, Armour received another report of seroconversion in the Netherlands. On 10 October, Armour learned of yet another seroconversion in the United Kingdom. Finally, on 13 December it was notified of a possible seroconversion in Chapel Hill, North Carolina. Additional clinical data about these cases were given to Armour in early 1986 and, by late February, Armour was aware that an article reporting the Chapel Hill case had been submitted to *The Lancet*.

That same month, at an AIDS conference held in Newcastle-upon-Tyne in Britain, Dr Peter Jones, the director of the Newcastle Haemophilia Centre, raised the first public questions about the efficacy of heat-treatment methods, suggesting that "complete AIDS inactivation cannot yet be guaranteed." Dr Jones cited four cases of probable seroconversion reported to him by U.S. and Dutch physicians. His remarks were reported in the British lay press and were the subject of several telephone calls to Armour's United Kingdom representatives from Dr Frances Rotblatt of the Medicines Division of the U.K. Department of Health and Social Security (the regulator of blood products). An article published in the 20 February 1986 issue of the *New Scientist* added its own cautionary note that "Armour heats its factor VIII in the dry state for 30 hours at 60°C – far less than Elstree [Britain's Blood Products Laboratory] recommends as safe."

Two letters reporting seroconversions associated with commercial heat-treated products were published in *The Lancet* in the spring of 1986. Neither identified Armour as the source of the suspect product. The first, published on 15 March, was from Dr Gilbert White and colleagues and reported the case in North Carolina. The patient had received no blood products from 1975 until June 1985, when he received heat-treated factor VIII concentrate. Dr White concluded that the case illustrated the urgent need for further studies of heat-treated factor concentrates to provide reliable recommendations for the safe treatment of hemophiliac patients. In the 5 April issue Dr W. van den Berg, Dr J.W. Ten Cate, and colleagues reported the results of a study of thirty-five HIV-antibody negative hemophilia patients in the Netherlands. Two of the patients had become HIV-antibody positive during the study. One had been treated exclusively with a heat-treated product of U.S. origin, including a batch of heat-treated concentrate of intermediate purity that was later found to have contained plasma from a donor who developed AIDS. Publication of this report had been expected by Armour, and it was internally circulated to company officials in the United Kingdom.

Both *Lancet* reports were read by members of the Bureau of Biologics as part of the bureau's routine monitoring of relevant scientific literature. Despite the second letter's reference to "heat-treated intermediate and high purity FVIII concentrate of American origin," the bureau made no effort to identify the implicated product or its manufacturer. As Dr Boucher explained, "We were watching the literature, but we were not doing an active post-market surveillance on these products." Instead, the bureau relied on the manufacturer to comply with its regulatory obligation to inform it of any evidence of seroconversion. "If they have an adverse reaction," said Dr Boucher, "they are required to report it to the Bureau." Given the "role that we took and what we expected and anticipated," he continued, the problem was "the failure of them [the manufacturers] to report [adverse] reactions to us."

The source of the seroconversions reported by Dr White and Dr van den Berg was the subject of a brief exchange published in the 14 June 1986 issue of *The Lancet* under the heading "Heat Treatment of Factor VIII Concentrate." Dr Ralph Rousell of Cutter Laboratories wrote:

Reports indicating transmission of active HIV should ... indicate in reasonable detail the duration of heat-treatment, the temperature applied, and whether the preparation was in a liquid or lyophilized state during such treatment, to allow meaningful conclusions about the safety of heated preparations.

In an editorial note which immediately followed Dr Rousell's letter, *The Lancet* reported that Dr White and Dr van den Berg "have informed us that heat treatment was, in both cases, at 60°C for 30h[ours] in a lyophilized state." Armour was the only U.S. commercial factor VIII fractionator that used this process.

Armour's response

The meeting of Armour's "recombinant DNA steering committee" in October 1985 has already been described. On 21 February 1986, again before the first published accounts, Armour's plasma executive committee met to discuss the reports of seroconversion it had received from the United States and the Netherlands. It also reviewed unpublished Meloy viral inactivation data indicating that

the heat treatment procedure currently employed by us (60°C – 30 hours) was not totally effective in eliminating added HTLV-III [HIV] from FACTORATE Concentrates. Furthermore, more rigorous conditions applied to Generation I (intermediate purity) FACTORATE concentrates also resulted in residual detectable levels of HTLV-III, although current as well as experimental conditions all were capable of inactivating virus in quantities equal to or greater than 10^5 organisms/ml.

The committee was told that for the better part of the year, beginning in April and May 1985, Armour had been screening (that is, testing) source plasma for HIV antibody before processing it into factor concentrate. Nevertheless, significant quantities of Factorate concentrate manufactured from unscreened plasma were still in distribution and inventory. Dr Terry, a member of the committee, recommended that all H.T. Factorate manufactured from unscreened plasma be withdrawn from the market. Instead, it was agreed that very senior Armour representatives would meet with Dr David Aronson, of the U.S. Food and Drug Administration's Office of Biologics Research and Review, to review the data and would attempt to obtain Dr Aronson's opinion of the adequacy of Armour's process.

This meeting occurred on 25 February 1986. The Meloy and Paul Ehrlich Institute findings were presented to Dr Aronson. Dr Terry had not yet undertaken his critical review of the latter study. Dr Aronson concluded that "the Meloy data, demonstrating elimination of at least 10^5 organisms/ml in Generation I product is satisfactory, and that [Armour's] current heat treatment process is adequate relative to HTLV-III [HIV]." Accordingly, the H.T. Factorate from unscreened plasma did not need to be withdrawn from distribution. Armour's records of this meeting contain no reference to the Prince studies. Dr Aronson was informed of seroconversion cases said to be associated with the Armour product in the Netherlands and the United Kingdom. He was personally aware of only one seroconversion case, that being Dr White's U.S. report. "Aronson's summary," as recorded and highlighted by Armour, was that "[t]here are no cases reported of *clear cut* conversion due to heat-treated products only" (emphasis in original). No similar meetings were held or proposed with officials of the Canadian Bureau of

Biologics during this period, nor were the results of the spiking studies or reported seroconversion cases that Armour gave to the U.S. Food and Drug Administration made available to the Canadian regulator or the Red Cross.

Armour's plasma executive committee met again on 27 February and concluded that there was "no reason to believe there was a problem with non-screened product" (that is, concentrate manufactured from plasma that had not been tested for the presence of HIV antibody), but because screening would produce a theoretically improved product, "we should do as much as we can to implement these improvements as quickly as possible." H.T. Factorate manufactured from plasma that had been tested for the presence of HIV antibodies (that is, "screened" plasma) was to continue to be distributed, and unscreened product would be voluntarily withheld "unless we only have that type of product to distribute." This process was described as a "voluntary withholding and not a withdrawal." It was agreed that when sufficient supplies of screened Factorate product were available in inventory, Armour would begin an exchange program of screened for unscreened product. Distributors and regulators (in particular, the Red Cross and the Bureau of Biologics) were not notified of Armour's policy until late June 1986, when Armour began its exchange program.

On 23 June all blood banks and treatment centres in the United States were sent a letter asking them to return all unscreened H.T. Factorate in inventory to Armour in exchange for concentrate that had been screened for HIV. The letter referred to three reports of possible seroconversion after treatment with H.T. Factorate (including the two cases reported in the March and April 1986 issues of *The Lancet*), and explained that "the circumstances surrounding each case prevent a definite conclusion regarding association of the use of the product with seroconversion." The Bureau of Biologics and the Red Cross were informed of Armour's intention to withdraw unscreened H.T. Factorate on 26 and 27 June 1986, respectively. This was the first formal notification the bureau had received of seroconversions possibly attributable to Armour's heat-treated product.

Dr Martin Davey, the assistant national director of the Red Cross blood transfusion service, passed the information to the Red Cross medical directors on 30 June in a memorandum in which he stated: "The CRC BTS [Canadian Red Cross blood transfusion service] feels that this withdrawal is unnecessary, but must comply with Armour's wishes." Some 813 vials of unscreened concentrate, representing approximately 400,000 units of antihemophilic factor, were returned to the national blood transfusion service office by 25 August.

Dr Robert Card, the chair of the Canadian Hemophilia Society's medical and scientific advisory committee, wrote to Dr Davey on 22 July 1986 to express the committee's concern that the Armour withdrawal had been limited to unscreened concentrate. The Bureau of Biologics was not sent a copy of this letter. In the letter to Dr Davey, Dr Card wrote: "Since all evidence to date indicates that heat treatment should destroy all HTLV-III [HIV] virus, there

is a concern that the methods used in Armour factor VIII by implication might not be effective." He asked the Red Cross to obtain and give the Canadian Hemophilia Society information from Armour about the heat-treatment method used in producing H.T. Factorate. In a letter dated 31 July to Dr Michael Rodell, Armour's vice-president of regulatory affairs, Dr Davey wrote that "Dr R. Card has written (attached) expressing concerns of the CHS [Canadian Hemophilia Society], which we share, about the heat-treatment of your concentrate, and asking whether you have modified your process, or intend to do so as a consequence."

No response to Dr Davey's letter has been located. Armour's submissions to the Inquiry assert that there is no copy of Dr Davey's letter in Armour's files and that Dr Rodell does not recall receiving it. Armour repeatedly declined to make witnesses available, and Dr Rodell would not testify at Inquiry hearings or consent to be interviewed by Inquiry investigators or counsel. "In any event," as Armour noted in written submissions, the Canadian Red Cross Society "appears to have continued to accept and distribute Armour concentrate without further assurances by Armour." During discussions between the Red Cross and Armour, the Red Cross learned that Armour was "actively considering a modification to their process to extend the time of heat-treatment" as a result of the reported cases of seroconversion. While recognizing that "even Armour is questioning the efficacy of its process and is looking at changes" during the summer and early fall of 1986, the Red Cross did not stop purchasing Armour's factor VIII concentrate, effect a withdrawal of all the short-heat Armour concentrate in distribution in Canada, or remove the product from its national or local inventory.

Armour's response in the United Kingdom

The reports of seroconversion had prompted a more immediate response in the United Kingdom. Immediately after Dr Jones's address to the Newcastle-upon-Tyne AIDS Conference in February 1986, Dr Rotblatt of the Medicines Division of the U.K. Department of Health and Social Security asked Armour officials for information about the case in the Netherlands. She also asked for confirmation that all Armour products distributed in the United Kingdom had been produced from screened plasma. After Dr Jones told her there were in fact two cases of seroconversion in the Netherlands, Dr Rotblatt, on 17 February 1986, asked Armour for additional information, including viral inactivation data. The next day, Dr Jones wrote to the medical assessor of the Committee on Safety of Medicines (an adjunct to the U.K. regulatory agency) recommending that "the Armour material should be withheld [from further distribution] until its safety can be endorsed" by the committee.

Departmental and Armour officials met to review viral inactivation data and possible seroconversion cases on 3 March. The Dutch and U.S. seroconversion cases were discussed and the Paul Ehrlich Institute and Meloy data

summarized; there is no reference to the Prince studies in the Armour memorandum of the meeting. Dr Rotblatt said that she had spoken with Dr Aronson and, as recorded by Armour, said "that our [Armour's] position was consistent with that appreciated by the FDA [U.S. Food and Drug Administration]."

As had occurred two weeks earlier in the United States and Canada, Armour began a voluntary product exchange of unscreened H.T. Factorate in the United Kingdom on 11 July 1986. A week earlier, British Armour officials had been given advance notice of the possible publication of a report of the seroconversion of a six-year-old severe hemophiliac ten or thirteen months after he had started treatment with unscreened H.T. Factorate. By early August, further investigation determined that "the time frame is such that the patient could have been infected with NHS [National Health Service] non heat treated product" before he began using Armour's H.T. Factorate. The case was now described as "borderline" and there was no longer an intention to publish it. Senior Armour officials in the United States were kept abreast of the situation, but, again, the regulatory agencies in the United States and Canada were not informed.

On 29 September 1986, Armour officials in the United Kingdom received a telephone call from Dr Frank Hill of Birmingham Children's Hospital. He told them of two new seroconversion cases, both implicating unscreened H.T. Factorate. Armour notified Dr Rotblatt of these new seroconversions the same day. Within one week, and after consultation with the Department of Health and Social Security, Armour voluntarily withdrew all unscreened and screened Factorate products from the United Kingdom and suspended any further sale of the product in that country. It also relinquished its product licences for all Factorate products there. A press release announcing the Armour withdrawal from the United Kingdom was sent to the Bureau of Biologics and the Canadian Red Cross on 7 October. Two days later the bureau informed the Canadian Blood Committee of the Armour withdrawal from the United Kingdom.

On the same day, Armour representatives met officials of the U.S. Food and Drug Administration's Office of Biologics to discuss the product withdrawal in the United Kingdom. According to Armour memoranda, staff of the Office of Biologics concluded that there was insufficient information to warrant a product withdrawal in the United States. Armour told its international representatives, including those at Rorer Canada, that information regarding the United Kingdom cases would be provided to regulatory authorities in countries where Factorate was licensed. Armour also told them that the U.S. Office of Biologics planned to convene a panel of experts to review the British seroconversions and to evaluate the need for further action. Rorer Canada was informed of this decision on 9 October.

The Canadian response

At the time of Armour's withdrawal of H.T. Factorate in the United Kingdom, the Red Cross's seventeen blood centres held four million units of screened H.T. Factorate; the national office had an additional three million units in stock; and the Red Cross had contracted to receive an additional seven and a half million units by the end of 1986. Recall of the products from the centres was not regarded as practicable at first, because only a small quantity of replacement factor VIII concentrate was available from the Red Cross's other regular suppliers, Cutter and Connaught Laboratories Limited. Efforts were made to obtain alternative supplies. On 9 October 1986, the Bureau of Biologics told the Canadian Blood Committee, the funding agency for the national blood program, that Cutter and Hyland could supply seven million and two million units of antihemophilic factor, respectively, and that an order for six lots of two million units each of H.T. Factorate from Armour had been cancelled. On 10 October, Dr Roger Perrault, the national director of the blood transfusion service, told the Canadian Blood Committee that the Red Cross had placed an order with Cutter for seven and a half million units of factor VIII concentrate and expected delivery the next week. The Red Cross had also told its centres to withhold further distribution of Armour factor VIII concentrate.

On the same day, a conference call took place between representatives of the Canadian Hemophilia Society, the Red Cross, and the Bureau of Biologics to discuss the question of a recall of all H.T. Factorate. The Red Cross proposed a full product withdrawal, expressing ethical and legal concerns about not doing so quickly. The Bureau of Biologics asked the Red Cross to delay a decision until the U.S. Food and Drug Administration had met to review the British seroconversions. A second conference call was therefore arranged for the next week. The Canadian Blood Committee was kept informed of these developments by Dr Perrault, who "reiterated the Red Cross' concern about product safety and the need to act now."

By 14 October 1986, all Red Cross blood centres had received replacement stock for Armour antihemophilic factor concentrate and all shipments of Armour factor VIII concentrate to hospitals had been suspended. On that day, the Canadian Blood Committee received another call from Bureau of Biologics officials to say that they had received information from the British government about the seroconversion cases there and were inclined to recall the Armour product. The bureau pointed out, however, that the U.S. Food and Drug Administration had yet to render a final decision on the question of recall, and that a recall in the United States would likely result in an embargo on the export of all other U.S.-produced antihemophilic factor concentrate and ultimately in shortages internationally. On 15 October, after discussions between the Bureau of Biologics, the Red Cross, and Dr Card (as the chair of the medical and scientific advisory committee of the Canadian Hemophilia Society), it was agreed that no action should be taken until after the meeting convened by the U.S. Food and Drug Administration for the next day.

The Food and Drug Administration decided to recall only unscreened factor concentrate – the product Armour had voluntarily exchanged for screened H.T. Factorate three months earlier, in late June and July. The next day, 17 October, the Canadian Red Cross received a letter from Dr John Furesz, director of the Bureau of Biologics. The letter in its entirety read:

Following our review of the available scientific data, we concluded that the [Armour heat-treated] product, when prepared from plasma screened for HIV antibodies, is considered non-hazardous with respect to HIV infection in hemophilia patients. Consequently, we advise you to continue with the distribution of this product.

To Dr Davey, the acting national director of the blood transfusion services, it appeared “a very clear statement – surprisingly clear, given the controversy of the previous week.” Accordingly, on 20 October Canadian Red Cross blood centres once again began to issue Armour antihemophilic factor. Two days later, Dr Davey wrote to the blood transfusion service medical directors, attaching a copy of the bureau’s letter and adding that the Red Cross supported the bureau’s position. Dr Davey testified that he was “very influenced in this by the fact that this proposal came so firmly from Dr Furesz and so directly after his consultations at a level in the United States to which we [the Red Cross] didn’t have direct access.”

During the hearings, Dr Furesz was asked the following question about his letter of 17 October:

... given, at that point, the history of Armour’s seroconversions and withdrawals, given the United Kingdom’s rejection of the product, given questions that had been raised about [Armour’s] heat treatment process itself, given the CRC [Canadian Red Cross] desire for withdrawal, and given in particular the fact that by that time the CRC had enabled itself somehow to provide complete replacement product for the Armour product it wished to have withdrawn, why – if there was going to be any risk of error at all – why would one not err on the side of caution and simply permit the Red Cross to pull the product?

“We looked at all the data which were available at that time,” Dr Furesz replied, and “we came to the conclusion that all those cases which were described were all from non-screened plasma.”

There remained, however, the risk inherent in the “window period” during which infected plasma would be undetected through HIV-antibody tests and could contaminate the plasma pools from which factor concentrates were manufactured. The question whether Armour’s viral inactivation process was sufficiently effective to eliminate that danger was still unanswered. Given the alarms that had been raised about the Armour factor VIII concentrate and

the procurement of adequate replacement product, Dr Furesz was asked, "Why not just say, 'That's it, we don't have to take this chance any longer'?" Dr Furesz explained that the bureau's confidence did not rest only on the conclusion that the seroconversions were caused by unscreened plasma:

That was one part; the other part was our confidence still in October 1986 in the inactivation procedure ... [W]e had no evidence at that time that [Armour's] heat inactivation procedure was inefficient. And this was shared ... by the FDA [U.S. Food and Drug Administration] as well, and they came to the same conclusion in cooperation with CDC [Centers for Disease Control] as we did, so ours was not at variance.

Dr Furesz observed, however, that "the real test comes in the field," and "unfortunately, it did not work the way everybody at that time [October 1986] thought was a proper way."

In October 1987, a year after the bureau's decision, several HIV seroconversions among hemophiliacs in British Columbia were reported. They were attributed to three lots of Armour H.T. Factorate. The Bureau of Biologics had approved two of these for sale on 28 October 1986, and the third on 9 December 1986. "With hindsight," Dr Furesz reflected, "everything is 20/20." The Bureau of Biologics knew, however, in October 1986 that of the two heat-treated products then distributed in Canada, all the internationally reported seroconversions were attributed to the one manufactured by Armour.

Withdrawal of other unscreened factor concentrate in Canada

Dr Card was immediately informed of the bureau's decision authorizing the continued distribution of screened H.T. Factorate. That same day, 17 October 1986, he was also informed that "all AHF [antihemophilic factor] in the Canadian system" came from plasma that had been screened for HIV antibody. Dr Davey conveyed the same information to the Red Cross medical directors in a memorandum dated 22 October 1986: "[A]ll AHF [antihemophilic factor] now available for distribution by CRC [Canadian Red Cross] has been prepared from anti-HIV negative [that is, screened] plasma." Copies of this memorandum were sent to Dr Furesz and to Dr Card. Dr Furesz, in turn, expressed a similar understanding in subsequent briefing papers prepared for the office of the deputy minister of the Department of National Health and Welfare.

On 31 October 1986, Dr Card asked the executive director of the Canadian Hemophilia Society to distribute copies of Dr Furesz's 17 October directive and Dr Davey's 22 October memorandum to the members of the society's medical and scientific advisory committee and to the directors of Canadian hemophilia clinics. In an accompanying newsletter, Dr Card reviewed the controversy surrounding the recent reports of seroconversions and, relying

on the information he had received, concluded: "Fortunately all products in Canada at the moment come from screened donors and we have not had to take the measure that was taken in the U.S. to withdraw non-donor-screened products [which were still in the system]." Dr Card expressed a similar view in his 31 October letter to a vice-president of the Ontario chapter of the Canadian Hemophilia Society. Reviewing the recent events in the United Kingdom and the response of the Bureau of Biologics to them, Dr Card wrote:

The BOB ... felt that a withdrawal of all products could not be undertaken and that the main thrust would be to ensure that all products issued were from screened donors, which fortunately from the Canadian standpoint has been the case for some time (but has not been in the U.S.).

Physicians treating hemophiliacs were not complacent. They advised each other of the need for "ongoing surveillance." Dr Card, in a letter dated 31 October 1986 to the Canadian Hemophilia Society's representative on the advisory subcommittee of the Canadian Blood Committee, stressed that "[i]t is important that the Bureau of Biologics and CRC BTS [Canadian Red Cross blood transfusion service] identify with great haste any potential problems in methodology for heat-treating of factor concentrates." However, the physicians tended to proceed on the assumption that all heat-treated products were relatively safe so long as they were manufactured from plasma that had been screened for the presence of HIV antibody. And, as Dr Irwin Walker, the chair of the medical and scientific advisory committee of the Ontario chapter of the Canadian Hemophilia Society, reminded his colleagues on the national committee in a January 1987 memorandum: "All blood products distributed in Canada are derived from screened plasma."

Within the month, however, hemophilia physicians learned that their confidence had been misplaced. On 5 February 1987, Dr Gershon Growe, the medical director of the comprehensive-care clinic in Vancouver, conveyed his concern to the medical director of the local Red Cross blood centre. "It was my expectation," he wrote, "that all of this [unscreened] material was removed from the market ... I would appreciate it if you would look into this matter and advise me as to how much longer we might have to put up with non source screen[ed] product." On 16 February, Dr Card wrote to Dr Davey:

I am writing as the Chairman of the Medical and Scientific Advisory Committee (MSAC) of the Canadian Hemophilia Society. It has recently been brought to my attention that there may remain in circulation in Canada a small amount of factor concentrate which has been prepared from donors who were not screened for anti-HIV antibodies. In the discussions that took place in October 1986 regarding the safety of Armour factor VIII, I had understood that there were no factor concentrates prepared from unscreened donors still in the system, as per your note of October 22, 1986.

I realize now, as per our telephone conversation of February 13th, that whereas there was no such material in the Blood Transfusion Centres that, in fact, there was a small amount remaining in circulation, having already been issued ...

I strongly believe that all factor concentrate that is currently in the system and has been prepared from blood donors who were not screened for the anti-HIV antibody, should be recalled. I have discussed this with a number of the members of MSAC, and there is unanimous agreement regarding this. Since such material does not appear to be in the Red Cross Centres, but is rather in the hospitals and/or hemophiliacs' homes, then the fan out system ... beginning at the CRC BTS [Canadian Red Cross blood transfusion service] Centres, would be necessary.

I recognize that at this point in time such a recall may lead to anxiety and fear among some hemophiliacs, but that does not change the necessity ... I recognize that such a withdrawal would add extra expenses to the system, but I firmly believe that this must be done.

Dr Card testified that, when he wrote the letter, his understanding was that no unscreened product remained "within the Red Cross distribution system, but that some had moved on from there to hospitals or to in fact ultimate users." This is why he proposed a withdrawal system that "fanned out" from the blood centres to the users of these factor concentrates.

Dr Davey replied within a matter of days. "As requested," he informed Dr Card in a letter dated 19 February 1987, "the Canadian Red Cross Blood Services will now take discreet steps to withdraw any such product remaining in Canadian distribution." He asked Dr Card to inform Canadian hemophilia physicians of the pending withdrawal.

Dr Card wrote to the members of the medical and scientific advisory committee and the hemophilia clinic directors on 4 March. In a memorandum, to which he attached both his February letter to Dr Davey and Dr Davey's reply, he wrote:

Whereas in October it was understood there was no further unscreened concentrates within the Red Cross distribution system, unfortunately, and none of us had realized this, there are some lots that have been issued and may be in hemophiliacs' hands or in hospitals. Because of recent developments I think there is no doubt that this should all be recalled as per my letter and I thank the members of MSAC who brought this matter to my attention as soon as it became apparent.

The unscreened factor concentrate that remained "in the system" was of Cutter manufacture. It included factor VIII and factor IX concentrates custom fractionated for the Red Cross from Canadian donor plasma, and "commercial" factor VIII manufactured by Cutter from plasma obtained from

U.S. plasmapheresis centres. Cutter had begun implementing HIV-antibody screening in April 1985, and by July all new plasma used in the production of its commercial preparations had been screened. This screening protocol was included in the labelling of Cutter factor VIII and factor IX products distributed in the United States as of 24 October 1985. At that date, the Red Cross had not yet fully implemented its testing of blood donations and stored plasma for HIV antibody and it knew that, because of the time required for processing, there would be a delay of some months before concentrate would be available from screened Canadian plasma. The Red Cross was kept informed of Cutter's activities and asked that, on the commercial preparations it bought from Cutter, "anti-HTLV [HIV] screening not be mentioned in the product labelling until Cutter/CRC [custom-fractionated] Product from screened [Canadian] plasma is available." Cutter was notified of the availability of screened Canadian plasma by letter on 7 February 1986:

This letter is to confirm officially that all Canadian Red Cross plasma delivered to Cutter Laboratories for fractionation will have been tested and found non-reactive for anti-HTLV-III [HIV] antibody by a FDA approved test method, commencing with the plasma shipment scheduled to leave Toronto on February 11th, 1986.

Delivery to the Red Cross of custom-fractionated concentrates bearing labels stating that they had been made from screened plasma was scheduled to occur by June or July 1986. After that date, all Cutter-manufactured concentrate destined for Canada was derived from plasma screened for HIV antibody.

The Red Cross's blood products services notified the local medical directors of a "voluntary replacement" program involving Cutter concentrates on 27 February 1987. Product replacement notices were in turn distributed to hospital blood banks and hemophilia program directors in early March. They listed thirty-four Cutter lots produced from unscreened plasma and asked for the return of vials from those lots.

Within days, Dr Walker was told by a member of the Canadian Hemophilia Society that some of the lot numbers involved in the Red Cross product replacement notice had been distributed in Ontario no more than six weeks previously. In fact, contrary to the treating physicians' understanding since late October 1986 that only screened factor concentrate was being distributed in Canada, Cutter factor IX concentrate from a lot identified as produced from unscreened plasma had been routinely distributed to regional Red Cross blood centres from the national Red Cross inventory until mid-January 1987. Dr Card was "shocked" to learn this when he saw the national inventory records for the first time during the course of his testimony at the Inquiry hearings; those records did "not match at all the information that we [the hemophilia-treating physicians] had as of ... October [1986]," he said.

Factor IX concentrate from several lots listed as unscreened in the product replacement notice were distributed by some Red Cross blood centres to regional hospitals through the late autumn of 1986 and the winter and early spring of 1987. Dr Card's strongly worded letter of 16 February, in which he urged Dr Davey to employ the "fan out" procedure to recall all unscreened factor concentrates, rested on his understanding, derived from his conversations with Dr Davey, that there was no such material in the blood centres. The February voluntary replacement notices issued to the local centres by the Red Cross said nothing to disturb this understanding. Yet at least one centre continued to distribute Cutter factor IX concentrate listed as unscreened as late as 27 May 1987, some three months after Dr Davey had assured Dr Card that "the Canadian Red Cross Blood Services will now take discreet steps to withdraw any such product remaining in Canadian distribution."

Dr Card had expressed his frustration with the information he was receiving from the Red Cross long before he saw the national inventory records at the Inquiry. Reporting on 25 March 1987 to Canadian hemophilia clinic medical directors about problems affecting the safety and security of the blood product supply, he had described communications between the Canadian Hemophilia Society, its medical and scientific advisory committee, Red Cross medical directors, and the Red Cross blood transfusion service as "less than ideal." In a letter dated 24 November 1987 to Dr Kaiser Ali, who had succeeded him as the chair of the national medical and scientific advisory committee of the Canadian Hemophilia Society, Dr Card described his "discovery that there may have been non-screened products still available after October 1986" as "extremely distressing." "Looking back," he testified, "one then has to question whether the information [received from the Red Cross] that we were trusting in was valid."

Modifications in Armour's heat-treatment process

On 16 October 1986, Armour applied to the U.S. Food and Drug Administration for approval of a modified viral inactivation process in which its vials of lyophilized (freeze-dried) concentrate were heated at 68°C for seventy-two to seventy-seven hours. Supporting documents demonstrated a 7.4₁₀ log reduction in HIV. The requested amendment to Armour's product licence was approved on 2 January 1987. Four days later, an internal company memorandum "advised" Armour's senior staff that "we are no longer licensed to heat treat at 60°C/30 hr." The final four lots of H.T. Factorate manufactured using that method were sent to Canada to meet contractual requirements for January and February 1987 and were distributed to local blood centres by the Red Cross in the spring of that year.

In March 1987, in a letter to the nurse coordinator of the comprehensive-care clinic in Vancouver, Dr Davey, then the acting national director of the Red Cross blood transfusion service, said, "[t]here is still an inventory of Armour

HT AHF [heat-treated antihemophilic factor] for distribution, and no reason to believe that it is not safe and effective." Dr Davey's statement about the product's safety was consistent with the conclusions of a survey of HIV seroconversions at hemophilia treatment centres outside the United States that had been conducted by the U.S. Centers for Disease Control and published in its *Morbidity and Mortality Weekly Report* that same month. The writers of the report observed that "[n]o cases of seroconversion among patients using only donor-screened [that is, tested for HIV antibody], heat-treated products have been reported to date." Noting, however, that the "distribution of seroconversion latency periods for hemophilia patients is not known" and that "less than a year has elapsed since most of the [clinics] surveyed began administering donor-screened, heat-treated factor concentrates," the Centers for Disease Control suggested that "[f]urther longitudinal studies ... may substantiate the additional margin of safety provided by screening donated plasma for HIV antibody."

It was not until April 1987 that Armour applied in Canada and the United Kingdom for licence amendments to include the 68°C/seventy-two-hour heat treatment. On 9 June, Dr Synek, who had conducted the initial review for the Bureau of Biologics of Armour's previous H.T. Factorate application, completed a preliminary review for the bureau of the information provided by Armour about its modified process. Armour's studies, he noted, showed that lyophilization contributed a 2.5 log₁₀ reduction in LAV and that heat treatment at 68°C for seventy-two hours resulted in an additional LAV reduction of 4.9 log₁₀. However, because of the high sensitivity of the assay method and the high initial titre of the virus used to spike the sample, residual virus was still detected at a low level in both intermediate and high purity products after the heat treatment. Armour withdrew its Canadian and United Kingdom licence applications for its 68°C/seventy-two-hour treatment in January 1988, and the modified procedure was never licensed in either country. Armour's short-heat H.T. Factorate remained on the list of approved products accompanying the licence renewal the Bureau of Biologics granted annually to Armour until April 1994, although this product was not distributed in Canada after the autumn of 1987.

New seroconversions in western Canada

On 5 October 1987 Dr Growe wrote to Dr Ali, then the chair of the Canadian Hemophilia Society's medical and scientific advisory committee, to inform him that five of the hemophilia patients at the Vancouver comprehensive-care clinic had HIV-seroconverted between May and August of that year. The seroconversions had been discovered through Dr Tsoukas's multicentre study. The patients had been treated with factor concentrates manufactured by Armour and Cutter, the only fractionators then supplying the

Canadian market with antihemophilic factor concentrates. On 19 October, Dr Tsoukas confirmed a sixth case. All were in the Vancouver area and all but one of the patients were children. No similar cluster of recent HIV seroconversions had been reported elsewhere.

Dr Ali spoke directly to Dr Brian McSheffrey, then the acting national director of the Red Cross blood transfusion service, about these cases by telephone the following day, 20 October 1987. On 23 October, the blood products subcommittee of the Canadian Hemophilia Society's medical and scientific advisory committee formally recommended to the Red Cross that all Armour and Cutter products be recalled. The Red Cross informed the medical and scientific advisory committee that it required "hard data on lot numbers and serology results in order to proceed." Dr Ali immediately made arrangements to have this information relayed to the Red Cross. Dr Tsoukas supplied additional data to the Red Cross and the Bureau of Biologics on 28 and 29 October. Approximately two weeks later, the Red Cross was told of an additional case of seroconversion; a hemophilia patient in Edmonton had tested HIV positive after treatment with Armour and Cutter concentrates within the previous ten months.

The evidence of the time when the Bureau of Biologics was first alerted to the British Columbia seroconversions is conflicting, but whenever it occurred the information was not passed from the Red Cross to the bureau in the week after Dr Ali's telephone call to Dr McSheffrey on 20 October. At the time, the Bureau of Biologics was unlikely to receive information from the Canadian Hemophilia Society directly because there was then no formal or even routine liaison between the bureau and the society or its medical and scientific advisory committee.

Despite assurances that only screened antihemophilic factor had been distributed in Canada during the past year, personal experience and distrust of manufacturers' pronouncements led hemophilia physicians and the medical and scientific advisory committee to identify the use of unscreened plasma – not concentrate produced by Armour's short-heat method – as the most likely cause of these seroconversions. Although Dr Card had earlier expressed concerns about possible shortcomings with the Armour heat-treatment process, Dr Ali testified that "that information was not made available to me" when he became the chair of the medical and scientific advisory committee in May 1986.

The Red Cross and the Bureau of Biologics met on 4 November 1987 to review the information then available. They agreed that the implicated Armour and Cutter products would be voluntarily withdrawn by the Red Cross without a formal "recall" notice, and Dr Ali was informed of this decision. The explanation for the nature of the withdrawal appears in a letter dated 12 November 1987 from Dr J.F. Riou, the director of the Bureau of

Field Operations (the arm of the Health Protection Branch that, among other responsibilities, enforces formal recall directives) to Dr David Pope, the assistant director of the Bureau of Biologics. Dr Riou wrote:

This will confirm our understanding that the products involved ... do not represent a health hazard, nor do they violate any of the provisions of the Food and Drugs Act and Regulations.

This action is therefore considered to be a product withdrawal and does not require involvement by this Directorate.

Should you disagree with this understanding, or if you felt that our assistance was required, please let me know immediately.

Although the letter bears Dr Pope's "Received" stamp, there is no evidence that he or any other member of the bureau ever replied to it.

On 4 November, the Red Cross, in a memorandum headed "Product Replacement," instructed the medical directors of its seventeen blood centres to "follow standard recall procedures by contacting your hospitals and requesting that they, in turn, contact the [hemophilia] patients in their area to obtain any product remaining from these lots." The Red Cross provided a list of the "implicated" lot numbers to be withdrawn, among them screened Cutter concentrate, unscreened Cutter product that had been the subject of a voluntary replacement in February 1987, and unscreened Armour concentrate manufactured after the exchange of screened for unscreened factor VIII concentrate in June 1986. A supplemental replacement notice was issued on 13 November extending the product replacement to include additional lots of Cutter factor VIII and factor IX concentrates and one lot of Armour factor VIII concentrate. Another Red Cross replacement notice was issued on 18 November, instructing medical directors to include two additional lots of Cutter factor VIII concentrate and one lot of Armour factor VIII concentrate that had been implicated in another case of seroconversion.

On 1 December 1987, Armour notified all U.S. blood bank directors and hemophilia centre directors that it was withdrawing the 208 lots of H.T. Factorate that had been manufactured using the 60°C/thirty-hour heat-treatment process and that still remained in distribution in the United States. The action was taken in response to reports of seroconversions in Canada and the United States. The British Columbia reports were, according to Armour, the first it had received of seroconversions ostensibly associated with the use of heat-treated concentrate manufactured from screened plasma.

Finally, on 10 December 1987, the Health Protection Branch announced the formal "class I" recall of three specified lots of Armour H.T. Factorate from the Canadian market. A "class I" recall is initiated only when the branch has established that a health hazard exists. In this case, the branch had identified the three specified lots (each of which had been subject to withdrawal

notices issued by the Red Cross in November) as directly implicated in the seroconversion cases in British Columbia. These lots were distributed only in Canada. Among those who seroconverted, their first infusions from these lots were given between 20 January and 28 April 1987. The branch's internal recall form refers to "inadequate heat-treatment process" as the reason for recall. The next day, Armour told the Red Cross it was withdrawing in Canada all H.T. Factorate that had been heat treated at 60°C for thirty hours; this was ten days after Armour had announced a similar withdrawal in the United States. Although most of this concentrate had been included in previous replacement notices issued by the Red Cross, thirteen lots were listed for the first time. There were five announcements related to the withdrawal or recall of H.T. Factorate in Canada between 4 November and 11 December 1987.

Dr Robert Remis, an epidemiologist with Quebec's regional bureau of infectious diseases in Montreal, was retained by Dr Alastair Clayton, then the director general of the Federal Centre for AIDS, in November 1987 to investigate the events surrounding the seroconversions in western Canada. He wrote to Dr Clayton on 21 December, with a copy to Dr Furesz at the Bureau of Biologics, expressing concern that the listing of three specific Armour lots in the class I recall order might be misleading. Dr Remis believed that the wording of the order implied that only these lots were implicated in the seroconversion cases, that hemophiliacs and their physicians could thus be falsely reassured, and that a less than vigorous recall of Armour lots might ensue as a result. His examination suggested that "the problem was more related to an inadequate process rather than any particular errors with these three above-mentioned lot numbers." Dr Remis's letter brought about no additional recall.

The cluster of seroconversions in British Columbia led regulatory officials in both Canada and the United States to examine Armour's production methods. During the first week of December, Dr Boucher of the Bureau of Biologics and Dr Remis visited the Armour plant in Kankakee, Illinois, to inspect the manufacturing facilities and production records. They found no manufacturing abnormalities in connection with the implicated lots. The U.S. Public Health Service inspected Armour's premises on 16–18 December and found no failure to follow the prescribed process associated with the production of the implicated lots or with the plasma pool used in their manufacture. No deficiencies were noted in the review of records relating to the product and control operations for the lots in question.

Dr Remis concluded nevertheless that the six British Columbia seroconversions were attributable to the use of the Armour product. Two other hemophiliacs who seroconverted in 1987 (one in Edmonton and a second in Winnipeg) also had received factor concentrate from one of the implicated Armour lots. Since Armour's records revealed no defects in the production of the implicated lots, Dr Remis's focus turned to the efficacy of the company's viral inactivation procedure. In a report to the Bureau of Biologics, he stated

that "the potential for [HIV] virus to survive the properly executed procedure using the shorter dry heat inactivation process [that is, 60°C/thirty hours] has been demonstrated and must be considered to be the most important finding in this investigation."

Dr Remis's conclusion followed his discovery that of the more than 2,000 donors who contributed units to the plasma pool from which the lots associated with the seroconversions were manufactured, seven tested positive on the preliminary screening test for HIV upon subsequent donations. An examination of Armour's donor records for several other lots showed that this result was not unusual. "The challenge to product safety," Dr Remis noted, "apparently lies in the donation of plasma shortly after HIV infection and before detectable antibodies are produced." To meet the "challenge" presented by the window period, Dr Remis recommended the use of products that had been submitted to more effective inactivation procedures, including pasteurization, heat treatment in steam vapour, and the use of chemical detergents and solvents – methods that afforded a wider margin of safety than dry heat-treatment processes. Dr Remis's study was published in the *Canadian Medical Association Journal* in June 1990. Another report of the seroconversions was published by Peter Neumann and colleagues in the March 1990 issue of the *Journal of Acquired Immune Deficiency Syndromes*. It also concluded that "it is apparent that the inactivation regimen for concentrates from this manufacturer [Armour] was inadequate," and suggested that longer heating periods at higher temperatures through vapour or "wet" treatment "may more effectively inactivate HIV."

On 15 December 1987, the Bureau of Biologics told manufacturers and the Red Cross that "wet" heat-treated products must be introduced "as soon as feasible." The next month, Armour stopped production of H.T. Factorate; instead, it decided to focus its efforts on the manufacture of a differently purified form of factor VIII which it distributed as "Monoclote." This product continues to enjoy wide distribution in the United States and other parts of the world. It has never been licensed for use in Canada.

The transition to "wet" treated concentrates; reducing the risk of AIDS and hepatitis

Dry heat treatment involves the heating of lyophilized concentrates after they have been placed in the sealed vials in which they will be commercially distributed. In the "wet" process, the heat treatment is carried out earlier while the coagulation factor concentrates are still in solution and before they are placed in individual vials and freeze-dried. In another "second generation" heat-treatment process, the lyophilized factor concentrate is heated through exposure to "steam" or "vapour" treatment under controlled pressure.

Support for wet heat treatment originated long before the HIV seroconversions of 1987. Until the advent of AIDS, the infection that was of primary concern to hemophiliacs and their physicians was non-A, non-B hepatitis, most

of which is now recognized as hepatitis C. Dry heat-treated products had been developed originally to reduce the risk of transmission of non-A, non-B hepatitis, but proved almost completely ineffectual against it. Dry heat treatment was much more successful in destroying HIV. Even before the recalls of concentrates in late 1987 resulting from HIV seroconversions, attention was returning to non-A, non-B hepatitis and to more effective means of viral inactivation. Before the end of that year, it was clear to the Red Cross, the Bureau of Biologics, and hemophilia-treating physicians that wet heat-treated products provided greater safety than those that had been dry heat treated, particularly with respect to non-A, non-B hepatitis.

In September 1985, *The Lancet* had published the preliminary results of a study that indicated that dry heating, while likely eliminating the risk of HIV transmission, had little or no effect on non-A, non-B hepatitis and that "heating factor VIII concentrate before final lyophilization (wet heating) is more effective in reducing the risk of post-transfusion [non-A, non-B hepatitis]." This article was distributed to members of the medical and scientific advisory committee of the Canadian Hemophilia Society and the medical and scientific advisory council of the U.S. National Hemophilia Foundation before they held a joint meeting in Houston that November. Wet heat treatment was the subject of some discussion at Houston and of increasing interest among Canadian hemophiliacs and their physicians over the next few months.

The Canadian Red Cross was being encouraged by hemophiliacs and their advocates to procure wet heat-treated concentrates. By the end of November 1985 Dr Derek Naylor, the director of the Red Cross's blood products services, told Dr Davey that "[t]here is increasing evidence that factor VIII concentrates heated in solution, as a slurry [semi-fluid mixture], or treated with steam, carry a reduced risk of transmission of hepatitis." He suggested that the Red Cross respond to requests from treating physicians and make limited amounts of wet heat-treated factor VIII concentrate available to newly diagnosed hemophilia patients for reasons of safety, "and also because it would improve the perception of the CRC [Canadian Red Cross] Blood Programme by the CHS [Canadian Hemophilia Society] and hemophilia patients in general." At its next meeting, on 3 May 1986, the Canadian Hemophilia Society's medical and scientific advisory committee asked for more studies on an urgent basis to settle the "important question" of the effectiveness of wet heat-treated products in inactivating the non-A, non-B hepatitis virus. Dr Card, the chair of the committee, wrote to the Red Cross at the end of that month asking that "wet" product be made available for a clinical trial and "for use in naive (never treated) hemophiliacs and in younger hemophiliacs who have only had cryoprecipitate with normal liver function tests who are being considered for conversion to concentrate [therapy] for their home care."

Dr Davey replied that the Red Cross was prepared to support a Canadian Hemophilia Society cross-Canada study by purchasing, for use in clinical

trials only, a limited supply of vapour-treated factor VIII concentrate from the European manufacturer, Immuno AG. At the time, Immuno's product was not licensed in Canada and was two or three times as expensive as the dry heat-treated concentrates that the Red Cross had already contracted to purchase. Arrangements were made with the Bureau of Biologics in early July 1986 to secure its immediate approval to distribute 200,000 units of the estimated one million units a year needed for the clinical trial, and these units were distributed for the naive users study on an "emergency drug release basis" pending formal licensing. Immuno's vapour-treated concentrate was formally licensed by the bureau in early August.

Until he had the results of the clinical studies, Dr Davey was not prepared to recommend a wholesale conversion from dry to wet or vapour heat-treated factor concentrates. He wrote: "There is no objective evidence that the method used by Immuno to prepare its concentrate is any more or less effective than those of other licensed manufacturers for inactivation of any class of virus." The Bureau of Biologics was also undecided. An internal bureau memorandum dated 30 December 1986 posed the questions: "Which is then *the most reliable way to prepare a viral safe AHF [antihemophilic factor] concentrate product?* Wet heat-treatment at 60°C/10 hours or dry heat-treatment at 68°C/seventy-two-hours?" [emphasis in original]. For the bureau, the answer lay in further experimental and long-term clinical studies. Canadian hemophilia physicians, however, were more convinced than the bureau was of the value of wet heat treatment. Their views are summarized in the minutes of the annual meeting of the Canadian Hemophilia Society's medical and scientific advisory committee in early May 1987:

Current viral inactivation techniques (dry-heating) when combined with donor screening were effective in virtually eliminating transmission of HIV virus. However, transmission of non-A, non-B hepatitis is not prevented by same. Prevention of non-A, non-B hepatitis was now of major concern for hemophiliacs ... There has been evidence that ... wet-heating processes may reduce non-A, non-B hepatitis transmission. Of concern is the cost and availability of such products.

The committee recommended that "for previously untreated hemophiliacs wet-treated products are the treatment of choice and should be made available."

Dr Ali, as the chair, presented the committee's views on the benefits of second generation products to the advisory subcommittee of the Canadian Blood Committee at its meeting on 14 October 1987. Dr Growe, who attended the meeting on behalf of the Canadian Hematology Society, expressed his concern about the recent HIV seroconversions in British Columbia resulting from the use of dry heat-treated products. "We must," Dr Growe said, "be able to respond ... with enhanced viral inactivation." Dr Ali echoed this position,

noting that the Canadian Hemophilia Society "would certainly endorse the setting aside of dry heat-treated concentrates in favour of newer products." Representatives of Connaught Laboratories Limited and Winnipeg Plasma Laboratory Inc. (formerly the Winnipeg Rh Institute), the Canadian fractionators, expressed some resistance to the quick adoption of enhanced viral inactivation technologies, as did, on scientific grounds, Dr Boucher of the Bureau of Biologics and Dr Wayne Sullivan, the chair of the advisory subcommittee and the Canadian Blood Committee's representative on it. Dr Perrault, then the deputy secretary general (operations), noted that "scientific rigors can be displaced by political pressures and ... the members [of the subcommittee] should keep this reality in mind." These "political pressures" soon found expression in a Canadian Hemophilia Society proposal to convene a consensus conference to examine blood product safety and advanced viral inactivation methods. The British Columbia seroconversions, as Dr Ali testified, had "galvanized and focused the whole thing and expedited that whole issue."

In the wake of the product withdrawals in late 1987, the Red Cross sought authorization and funding from the Canadian Blood Committee to restock its inventory of factor concentrates with "the newer enhanced viral inactivated" factor concentrates. "We are pulling material and we have to replace it," Dr Perrault testified, "so the time did seem ripe to convert." Full conversion, however, was not immediate. Because of availability difficulties, the blood products services division of the Red Cross blood transfusion service predicted in early December 1987 that full conversion to second generation heat-treated factor VIII and factor IX concentrates could not occur until the following March or April. The annual cost of full conversion was estimated to be more than \$20 million.

The Canadian Blood Committee approved an additional interim expenditure on 10 or 11 December 1987 to begin the conversion to wet heat-treated factor concentrates. The committee's decision came after learning Dr Boucher's "official opinion ... that the wet heat-treated Factor VIII provides 1 or 2 logs additional safety." Because of the greatly increased cost, however, the committee would not authorize the Red Cross to purchase the new concentrates without a written requirement from the Bureau of Biologics. The question whether to issue this requirement was described as "political" in a contemporary Health Protection Branch memorandum. The bureau was seen to "have no option but to require wet heat treatment." On 15 December, Dr Furesz, the bureau's director, gave the directive sought by the Canadian Blood Committee:

Recent reports on development of antibodies to human immunodeficiency virus in seronegative hemophilia patients have raised concerns about the adequacy of virus inactivation procedures being applied to antihemophilia factor products in lyophilized form.

In view of these circumstances the Bureau of Biologics has concluded that an already licensed, wet-heat process, generally recognized to be more effective in inactivating virus, be used. Accordingly the Bureau is recommending to blood fractionators that coagulation products treated with dry-heat be replaced as soon as feasible.

Dr Pope, the bureau's assistant director, was more direct in a letter dated 28 January 1988 to the Ottawa centre of the Red Cross: "I am writing to confirm that the Bureau of Biologics is now requiring that coagulation products shall be treated with a viral inactivation process that is more effective than the 'dry heat' methods that have been used to date."

By the time of the bureau's mid-December directive, it was clear that only four million units of vapour-treated or wet heat-treated factor VIII concentrate would be available for hemophiliacs in Canada in the first three to four months of 1988. The normal consumption of factor VIII concentrate in the same period was fourteen million units. As with the introduction of dry heat-treated products in 1985, it became necessary to develop guidelines to determine who would receive the limited supplies of wet factor concentrates during the conversion period.

An "ad hoc committee on the use of factor VIII" under the auspices of the Red Cross discussed this problem in a conference call on 17 December. Dr Walker, the director of a hemophilia clinic in Hamilton, chaired the meeting. The Bureau of Biologics, the Canadian Blood Committee, the Canadian Hemophilia Society, hemophilia physicians, and the Red Cross were all represented. The following priorities were established for distribution of wet or vapour heat-treated products: first, to previously untreated hemophiliacs and those who had received only cryoprecipitate in the past; second, to hemophiliacs who tested negative to HIV antibody. Candidates for the new products, Dr Ali subsequently informed hemophilia-treating physicians throughout the country, would have to be tested for HIV antibody. The Red Cross national blood transfusion service adopted the same position on 29 December in a directive to its blood centres that, in order to gain priority status, previous concentrate users "must have an anti-HIV test done." In a letter to a local hemophilia physician, Dr Roslyn Herst, the deputy medical director of the Toronto blood centre, wrote that, "[f]rom the defined priorities ... it is likely that only a limited number of adult severe hemophiliacs would be eligible until there is a greater supply" of the new product.

The Ontario chapter of the Canadian Hemophilia Society took strong objection on ethical and therapeutic grounds to the decision to make distribution of wet or vapour heat-treated product dependent on a patient's testing negative for HIV antibody. It was concerned that the policy would inevitably

risk compromising the confidentiality of patients' HIV status. A second concern was expressed by the chapter president in a letter to the national president of the society:

Hemophiliacs who have tested positive for the HIV virus and their families are already under tremendous stress and this decision only exacerbates the worry, anxiety and the constant panic that any symptom of illness brings.

These persons are the ones most likely to be suffering from the effects of previous hepatitis, arthritic joints and other infections caused by protracted use of contaminated product and if differentiation must be made we feel they should be high priority for the improved product.

The categorizing of hemophiliacs for the purpose of rationing factor products was based on poor judgement and should be amended immediately. We have had shortages of product before and it was handled by giving reduced amounts of supplies to families ... This practice must be continued. The treatment, whether product type or care, must not be based on HIV status but on the individual's medical needs.

By February 1988, the hemophilia-treating physicians had agreed that HIV designation was not the best approach to dealing with shortages affecting distribution of the new product. They preferred instead to leave decisions to the discretion of the medical directors of the various comprehensive hemophilia programs throughout the country. On 12 February, the ad hoc committee on the use of factor VIII concentrate agreed to an amended set of guidelines in which HIV sero-status was no longer the determining factor. Priority now was to be given to hemophiliacs who had never received blood products. Hemophiliacs then being treated with advanced viral inactivated factor VIII concentrate composed the second preferred category, and those whose previous treatment had been restricted to cryoprecipitate were third on the list. Distribution of the newer products beyond these categories was to be decided by the Red Cross medical directors in consultation with the local hemophilia clinic directors or other hemophilia-treating physicians, who were to keep in mind the age of the patient, the total amount of factor concentrate received in the past, and the patient's HIV status. This last consideration was described as "a sensitive issue in some locations," and Red Cross medical directors were each told that they might "wish to modify the criteria in consultation with the treating physician."

Despite general recognition of the enhanced protection afforded by wet heat-treatment, the replacement of wet for dry heat-treated factor VIII was "still under active consideration" by the Canadian Blood Committee in

mid-February 1988. A member of the committee, Dr Sullivan, set out the committee's concerns at the consensus conference on blood products held by the Canadian Hemophilia Society on 11 February:

I must tell you that cost is a real and legitimate issue to the Canadian Blood Committee and the provinces which fund these products ... The Committee has not yet reached a final decision on this issue. We are not yet convinced that a universal access to this product is essential.

The Canadian Blood Committee was still reluctant to finance universal access to wet heat-treated concentrates in mid-April. It discussed the use of current inventories and the acquisition of additional supplies of dry heat-treated factor VIII concentrate at a meeting on 21 and 22 April. The record of decisions of that meeting includes the following minute:

Noting the economic advantages of further acquisition of the dry product and the minimal additional risk in terms of HIV, NANB [non-A, non-B hepatitis], and Hepatitis B for the majority of hemophiliacs (already likely exposed), members were interested in interpreting the "as soon as feasible" caveat of the Bureau of Biologics (BoB) [15] December 1987 directive to mean when market forces have moved away from the dry product.

The committee agreed that its secretariat should draft, for review by the committee, an "appropriate letter" to the bureau reflecting these concerns. After extensive comment by the members of the committee, the final version, signed by the executive director, Dr Denise Leclerc-Chevalier, was telefaxed to Dr Furesz on 28 April. It sought "further clarification of your December 1987 directive that dry heat-treated coagulation factor products be replaced as soon as feasible."

Dr Furesz responded on 3 May 1988:

The position of the Bureau of Biologics regarding the use of dry heat-treated Factor VIII has not changed since the Bureau's directive to the Canadian Red Cross in December 1987. At that time we indicated that dry heat-treated product should be replaced as soon as feasible. It was our understanding that this would be not later than June 1988. While we see no objection to the use of current inventories of existing products which have been heated at 68°C for 72 hours, additional purchases are not desirable.

The Canadian Blood Committee authorized the expenditure in June, and on 15 July 1988 Dr Ali was assured by the Minister of National Health and Welfare that "as of today, there are no more dry heat-treated products in

inventory at the Red Cross." This was the most significant development in the safety of products used by Canadian hemophiliacs from the time of the conversion to heat-treated products in 1985 until the introduction of recombinant (genetically engineered) factor VIII almost a decade later.

Commentary

For Canadian hemophiliacs, the introduction of heat-treated factor concentrates in mid-1985 raised fresh hope for an end to their routine exposure to the risk of infection with HIV. That risk – and its consequences, a devastating toll in AIDS-related illness and eventual death – came from the use of non-heat-treated concentrates, on which the health of many hundreds of Canadians depended. As of 1 July 1985, hemophiliacs and their physicians could take comfort in knowing that they no longer had to choose between uncontrollable bleeding episodes, excruciating pain, an abbreviated life span, and a regimen that carried the risk of contracting a fatal disease with each injection. While they knew that no blood-derived drug could ever be entirely risk-free, most hemophiliacs who remained uninfected in mid-1985 believed that they had escaped the threat of AIDS and, in that respect at least, had moved into an age of safe and effective blood products. This belief was ended by the discovery that six hemophiliacs in British Columbia treated exclusively with heat-treated factor VIII concentrate had seroconverted in mid-1987.

Armour

The Armour Pharmaceutical Company was one of four U.S. commercial manufacturers of factor concentrates in the 1980s. It was required to keep the Bureau of Biologics informed of any matter relating to the safety of products for which it was seeking or had received a licence in Canada. It did not do so with respect to the heat-treated factor VIII concentrate it sold under the tradename H.T. Factorate.

In late June 1986, Armour notified the Red Cross and the Bureau of Biologics that it had decided to withdraw H.T. Factorate made from unscreened plasma and exchange it for H.T. Factorate manufactured from plasma screened for HIV antibody. This was Armour's first indication to the Canadian distributor and regulator that there was any reason for concern about the safety of its heat-treatment process. Armour had greater reason for concern than it conveyed at that time. Dr Prince's studies, conducted between January and August 1985, had cast doubts on the efficacy of Armour's short-heat process. Other confidential laboratory studies conducted in the autumn of 1985 and the first half of 1986 tended to confirm that heating lyophilized factor concentrate for longer times and at higher temperatures than Armour used in the manufacture of H.T. Factorate was, as reported in an internal memorandum, "much more effective in reducing infectivity." Armour knew that Dr Prince's assay was more sensitive than the assay developed by Dr McDougal, which had been used in earlier viral inactivation studies. Moreover, Armour's

concerns about its short-heat method did not arise exclusively from experimental data; it had been informed between July and December 1985 of at least five cases in Europe and the United States of seroconversion after the use of H.T. Factorate.

Armour had recognized by February 1986 that H.T. Factorate manufactured from screened plasma was at least theoretically safer than that produced from unscreened plasma. It decided not to withdraw all its unscreened product at that time. Instead, despite the information it had about the short-heat process, it waited until it had enough factor concentrate produced from screened plasma to allow it to conduct a product exchange in June and July.

Even before this product exchange, Armour could have begun to modify its heat-treatment process to one that used a temperature higher than 60°C for more than thirty hours. Armour considered, but rejected, a proposal to change its heat-treatment protocol as early as October 1985, after it had received Dr Prince's findings. It did not formally apply to the U.S. Food and Drug Administration for approval of a process of enhanced heat treatment until October 1986, after reports of Armour-related seroconversions had appeared in the medical literature. No similar application was filed with the Bureau of Biologics until April 1987. The new process had not yet been approved in Canada when the seroconversions in British Columbia were reported in October 1987.

After the seroconversions were reported in the United Kingdom in October 1986, Armour voluntarily withdrew all H.T. Factorate from that country. It took no similar action in Canada or the United States. Armour alone knew the results of its internal viral inactivation studies and all the information contained in the reports of seroconversion related to the use of H.T. Factorate. Although no seroconversions were attributed to the use of H.T. Factorate manufactured from screened plasma until the British Columbia cases in 1987, Dr Prince had told Armour of the "modest process efficacy" of its heat-treatment method as early as the autumn of 1985 and had warned Armour at that time that its process "is clearly not sufficient to yield sterile products." Armour could not be certain that screening its plasma would be effective in preventing contamination of its concentrates with HIV because of the window period of early HIV infection, during which the antibody cannot be detected. Indeed, as Dr Remis later learned from his review of Armour's own records, it was not unusual for plasma from some donors who were subsequently discovered to be in the window period to be included in the plasma pools from which H.T. Factorate was manufactured. The proper precautionary response, particularly after the seroconversions in the United Kingdom in 1986, was to stop distributing short-heat H.T. Factorate immediately and to withdraw all factor concentrate manufactured by that process voluntarily.

Armour was required to report promptly to the Bureau of Biologics any deficiency or alleged deficiency arising from the use of its products. Regulators of biological drugs rely on manufacturers to keep them informed of

possible danger to consumers, so they can make timely and informed decisions. Although Armour did convey some of the clinical and experimental information on which its concerns about possible residual viral contamination of H.T. Factorate were based to the U.S. Food and Drug Administration in February 1986, it gave no similar information to the Canadian regulator, the Bureau of Biologics. Armour did not inform the bureau of possible sero-conversions attributed to the use of H.T. Factorate until late June 1986; then, it did so in a form letter that accompanied the announcement of its product exchange. Armour never gave the bureau, or the Red Cross, reports or even summaries of its internal spiking studies, and those by Dr Prince, that cast doubt on the efficacy of its viral inactivation process.

Not only did Armour not transmit Dr Prince's data to the bureau but it prohibited Dr Prince from publishing his research on the safety of its products. Armour reasoned that the publication of Dr Prince's research "in isolation could only be confusing to the scientific community, the treatment community and the public." Armour was also concerned about the negative impact that publication of Dr Prince's findings could have on its competitive position. Armour's obligation was to convey safety-related information about its products to the bureau promptly. It could have addressed risk, if any, of confusion by including in a timely report to the bureau all the contradictory and inconsistent data it believed qualified Dr Prince's findings.

The Bureau of Biologics

The Bureau of Biologics was the regulator of the manufacture, importation, and distribution of blood products in Canada. It was responsible for setting minimum standards of quality and safety in the industry and for making reasonable efforts to ensure that those standards were met. Other institutions had important roles to play, but the bureau had the ultimate responsibility for ensuring that blood products licensed for distribution in Canada were "not unsafe."

In deciding to issue and renew a licence, the Bureau of Biologics relies on the integrity of the information given to it by the manufacturer. However, it can never delegate its responsibility to the manufacturer, even by default. Although the manufacturer and the regulator are both concerned about the quality and safety of a product, their interests are not the same. To the manufacturer, commercial considerations are an element in assessing tolerable risk. Thus, for example, in internal discussions about the implications of Dr Prince's data, one of Armour's officers argued that "the issue is not one of regulation, but rather marketing." The cost of new technology, the strength of the competition, the potential for liability, and the continued support of equity investors are matters to which any profit-directed corporation is sensitive. These are not considerations for the regulator. The Bureau of Biologics provides a service to Canadians. It has only one client – the public – and the safety of that client must remain its paramount concern.

In the routine review of an application for a product licence, the bureau could, and did, check samples of biological drugs for recognizable contaminants and to satisfy itself that specified and prescribed standards of biochemical activity and purity were met. There were many other tests and studies performed by the manufacturer that it did not replicate. For example, the bureau did not conduct laboratory experiments designed to test the effectiveness of a manufacturer's viral inactivation methods or clinical investigations to assess the long-term safety of new formulations. Neither the Food and Drug Administration in the United States nor the Department of Health and Social Security in the United Kingdom performed these studies. They were done by the pharmaceutical manufacturers themselves as part of the research and development involved in the manufacture and marketing of new drugs and in satisfying the regulators and the public that their products were safe. The Bureau of Biologics was dependent on the detailed reports of the procedures and results of the studies it received from Armour. This dependence should not have inhibited the bureau from reviewing them with a critical eye when information inconsistent with the results of those studies was published in the medical and scientific literature.

The bureau, it is true, did not have the benefit of the studies conducted by Dr Prince for Armour in 1985 or the seroconversion data reported privately to Armour that same year. However, it was aware that Armour's method of viral inactivation involved lower temperatures and shorter heating times than the processes used by several of its competitors. Reported studies showed a direct relationship between these variables and the efficacy of any heat-treatment method. When two accounts of seroconversions attributed to heat-treated factor VIII concentrate of U.S. origin appeared in *The Lancet*, a widely read and very accessible medical journal, in March and April 1986, the Bureau of Biologics made no effort to determine which fractionators were involved or whether the implicated products were the same as any distributed in Canada. Nor did it make any inquiries after the publication in *The Lancet* in May 1986 of Dr Prince's report of his experiments with commercial preparations heated at 60°C, despite Dr Prince's cautionary language about the use of such preparations. The bureau knew that only two fractionators heat treated concentrate at 60°C and that only one of them, Armour, produced a concentrate that was distributed in Canada. No inquiries were made even after the publication of the editorial note in *The Lancet* in June 1986 in which Armour's heat-treated factor VIII concentrate was identified in all but name as the product associated with both seroconversions reported a few months earlier. The bureau was responsible for assessing the safety of the viral inactivation processes used in manufacturing all blood products that were licensed in Canada. To carry out this responsibility, the bureau needed to know about significant developments affecting any class of products it licensed. Any article in the medical and scientific literature that addressed the efficacy of heat treatment should have attracted its attention.

With the withdrawal of Armour's Factorate products from the United Kingdom in October 1986, the bureau had a basis for concern that Armour's heat-treatment process might not completely eliminate the presence of HIV in unscreened plasma. The risk of HIV in the plasma used to manufacture concentrate was greatly reduced after Armour began using only plasma that had been screened for HIV antibody in manufacturing H.T. Factorate by the short-heat process, but it did not eliminate the risk. An HIV-infected donation that escaped detection because it was collected during the window period would contaminate the entire plasma pool from which the concentrate was being manufactured. Since the minimal infectious dose of HIV was unknown, the possibility remained of transmission of HIV through the resulting product. The question for the bureau after the withdrawal in the United Kingdom was not whether heat-treated concentrates fractionated from screened plasma were safer than those fractionated from unscreened plasma, but whether the heat-treated factor concentrates of some manufacturers – those that used a short-heat process – could still transmit HIV. The bureau's critical focus by October 1986 should have been on the process rather than the plasma.

Armour withdrew its factor concentrate from the United Kingdom and relinquished its licence there in October 1986 after reports of more seroconversions and after consultation with that country's regulator. By this time, the Bureau of Biologics knew that safety concerns were causing Armour to modify its heat-treatment process by moving to a higher temperature for a longer time. The Red Cross responded to the developments in the United Kingdom by urging a similar product withdrawal in Canada. It secured an adequate alternative supply of heat-treated factor concentrate within days. The Bureau of Biologics waited until the U.S. Food and Drug Administration decided to recall only factor concentrates manufactured from unscreened plasma. The bureau then pronounced Armour's H.T. Factorate "non-hazardous." The bureau went further than the Food and Drug Administration: it "advised" the Red Cross to continue distribution of the product.

The Bureau of Biologics must determine whether biological drugs are in compliance with the *Food and Drugs Act* and its *Regulations*. Decisions about whether a plasma-derived product should be licensed or whether a licensed product should no longer be distributed are appropriate exercises of the bureau's legal authority. There are times when, in the proper discharge of its mandate, the bureau must ensure that hazardous products are removed from the market. The bureau's letter of 17 October 1986 to the Red Cross was intended and construed as a directive from the regulator "to continue with the distribution of [H.T. Factorate]." Although the Red Cross did not need to defer to the bureau, the directive put it in a very difficult position. The bureau should not have discouraged the Red Cross from exercising its independent discretion to discontinue the distribution of a blood product that it had determined was unsafe.

The complete removal of H.T. Factorate in October 1986 would have prevented the cluster of HIV seroconversions among British Columbia hemophiliacs, whose first use of the implicated lots did not occur until early 1987. The Bureau of Biologics did not expect that this infection might occur when it directed the continued distribution of the product in October 1986, but it had not exercised its power as regulator to secure all the essential information. It had broad authority under sections C.08.007(a) and (c) and C.08.008(a) of the *Food and Drug Regulations* to request reports from Armour of all its records of "animal or clinical experience, studies, investigations and tests conducted by the manufacturer or reported to him by any person," and Armour's records of its own "experience, investigations, studies and tests involving the chemical or physical properties or any other properties" of H.T. Factorate. It made no use of this authority.

The Canadian Red Cross Society

When it learned of the withdrawal of Armour's H.T. Factorate from the United Kingdom in October 1986, the Red Cross showed that it could respond promptly and effectively to a potential danger. On previous occasions, as when both heat-treated factor concentrates and HIV-antibody test kits were introduced, it had not acted until it had the approval of the Canadian Blood Committee. On this occasion it did not wait for the committee's approval. Within days of receiving notice of the events in the United Kingdom, it suspended the distribution of Armour's factor concentrate in Canada, secured and supplied its centres with commercial concentrates that had not been implicated in any seroconversions, and urged a complete withdrawal of H.T. Factorate. In the end, however, it deferred to the Bureau of Biologics directive to "continue with the distribution of this product."

The Red Cross, as the distributor, retained an independent discretion to withdraw or recall products that it had decided posed a potential threat to the health or safety of Canadians. The exercise of this discretion was complicated, however, by the Red Cross's dependence on the Canadian Blood Committee to fund its blood program. After the bureau directed the continued distribution of H.T. Factorate, the Red Cross would have found it difficult to assert an independent position and recall the product unless it was prepared to risk absorbing the cost of the recall and exacerbating its already tense relations with the Canadian Blood Committee. These complications may explain but do not justify the Red Cross's reluctance to make an independent decision and act on it.

The Red Cross, like the Bureau of Biologics, was not aware of the results of Armour's internal spiking studies, nor was it told about the pre-publication reports of seroconversions attributed to H.T. Factorate. It did follow the medical and scientific literature, however. Like the bureau, it made no attempt to identify the manufacturer of the products associated with seroconversions

when they were reported in the professional journals. Nor did it independently ask the questions posed by Dr Card on behalf of the Canadian Hemophilia Society about the efficacy of Armour's short-heat process in inactivating HIV, or convey Dr Card's concerns to the Bureau of Biologics.

The Red Cross had more information about the safety of blood products than any other organization in the Canadian blood system. Too frequently, however, that information was not passed on to persons outside the senior membership of its own blood transfusion service. Despite Dr Card's earlier inquiries, the Red Cross did not tell him about Armour's plans to convert its viral inactivation process from short-heat to a process similar in time and temperature to that used by the other manufacturer with which the Red Cross had supply contracts.

Hemophiliacs and their physicians did not take part in the critical decisions about the supply of blood products, and their views on product preference were not solicited. Unlike persons with most diseases, hemophiliacs for all practical purposes had no choice in the products on which their health depended. Those who used factor concentrates were restricted to the few products bought and distributed by the Red Cross.

In the autumn of 1986, the Red Cross asked Cutter not to indicate on the label of the commercial factor concentrate it was buying that the product was manufactured from screened plasma. It asked Cutter to withhold that information until custom-fractionated concentrates made from Canadian screened plasma were ready to be sent to Canada. The Red Cross's explanation for that request was that there would be major problems if it were known that both screened and unscreened products were simultaneously available. It was concerned that a perceived difference in risk between the two products could increase demand for and, in turn, create shortages of the screened concentrate. The issue of differential risk should have been addressed directly by the Red Cross. If, as the Red Cross contended, heat treatment of factor concentrates was in itself effective in inactivating HIV, there was no reason to prevent Canadian hemophiliacs and their physicians from having the information that was available through labelling to all users of the same product in the United States. If, however, there was some basis for considering heat-treated factor concentrates manufactured from screened plasma to be safer than those manufactured from unscreened plasma, there was sound reason to communicate the information about the plasma source of each vial. Canadian hemophiliacs and their physicians needed this information in order to assess the therapeutic risk. Any potential problems in supply could have been addressed by setting the unscreened product apart for use only if the supply of the screened concentrate was exhausted or by establishing a transitional set of priorities for distribution of the screened concentrate, to be administered by the treating physicians.

The Canadian Blood Committee

The Canadian Blood Committee was kept informed of the Armour seroconversions, but it was not directly involved until after the December 1987 Armour recall when there was increasing pressure to convert to second generation, much more expensive, heat-treated concentrates. As the guardian of the public purse, the Canadian Blood Committee was properly concerned to ensure that any increased expenditure of public funds for these wet heat-treated products be justified by enhanced safety benefits.

The Canadian Blood Committee was the organization through which the elected provincial governments exercised financial control over an essential health care service – the provision of blood and its derivatives. The committee had no real independence. Its members were the representatives of the provinces that appointed them, and their actions – expressed primarily as decisions authorizing funding – reflected the interests and direction of the provincial ministers of health to whom they reported.

After the 1987 seroconversions in British Columbia, there was renewed concern about the transmission of non-A, non-B hepatitis through the use of dry heat-treated factor concentrates. The Canadian Blood Committee came under pressure from hemophiliacs and others to authorize the Red Cross to convert to factor concentrates manufactured with enhanced viral inactivation methods such as wet heat treatment. The cost of that conversion was considerable by any measure and, as a result, had potential political as well as budgetary implications for each province. Although the committee accepted the wisdom of the conversion in principle, it refused to authorize the necessary expenditure without a written directive from the Bureau of Biologics to replace dry heat-treated factor concentrates. The committee, in effect, used the regulator to make a policy decision. It then did nothing to implement the directive for six months. When the bureau directed the replacement of dry heat-treated products as soon as feasible, the committee should have seen that this was done.

The Decline of the Domestic Fractionation Industry

The ministers of health of the provinces agreed in December 1980 to support the development of three domestic fractionation plants, all of which were to operate on a not-for-profit basis. Their products were to be made from plasma collected by the Canadian Red Cross Society (Red Cross) and were to be distributed by the Red Cross. The three fractionators were to be Connaught Laboratories Limited (Connaught) in Ontario, the Institut Armand-Frappier (Armand-Frappier) in Quebec, and the Winnipeg Rh Institute (Rh Institute) in Manitoba. These developments are described in detail in Chapter 4.

The key to success as a fractionator in the 1980s was an ability to produce factor VIII concentrate. Although it experienced problems in production, Connaught made factor VIII concentrate during the 1980s. The Rh Institute and its successor, Winnipeg Plasma Laboratory Inc., never produced a marketable factor VIII concentrate. Armand-Frappier never built a fractionation plant. By the end of the 1980s, none of the three was making factor concentrate.

Connaught Laboratories Limited

At their meeting in December 1980, the ministers of health of the provinces agreed that Connaught should continue its existing fractionation operation and that it should receive 50 per cent of all Canadian plasma for processing in its plant. Connaught began producing non-heat-treated factor VIII concentrate for the Red Cross in 1981. On 16 November 1984, however, the Bureau of Biologics issued a directive to the manufacturers of fractionated blood products that "further reliance on AHF [antihemophilic factor] products that have not been heat treated cannot be justified and that such products should be replaced with heat-treated AHF as soon as feasible." At that time, Connaught was not licensed to make heat-treated factor concentrate. Ten days later, on 26 November, the Red Cross told Connaught that, although Connaught would be allowed to deliver non-heat-treated concentrate already in process until the end of March 1985, it would receive no more fresh frozen plasma for fractionation from the Red Cross until it had the ability to produce heat-treated factor VIII concentrate that was licensed by the Bureau of Biologics. The bureau's directive had the effect of suspending the key part of Connaught's

fractionation program until it obtained a licence for the new product. Representatives of Connaught attended the consensus conference held in Ottawa on 10 December 1984 to discuss the conversion to heat-treated concentrate. They estimated that their corporation would have a licensed heat-treated factor VIII concentrate by July 1985, but added that it was considering closing its fractionation operation. These events are described in Chapter 15.

The same day, after the conference, Connaught's representatives met with the members of the Canadian Blood Committee who were present. They repeated that Connaught was considering closing its fractionation operation within two to four years, and gave two reasons. First, although Connaught had secured an extension of its fractionation contract from the Red Cross, it was only until the end of 1985. Second, although Connaught supported the provinces' policy that domestic fractionation should be not for profit, it was committed, since its sale by the University of Toronto, to rapid growth as a profit-making enterprise. That commitment and its historical role as the Red Cross's not-for-profit domestic fractionator were not compatible. So that Canada would not be deprived of a domestic fractionator, Connaught was willing, however, to develop a heat-treated factor concentrate and to continue to produce fractionated products until the Rh Institute or Armand-Frappier was able to take over its role.

The representatives of Connaught also expressed a concern about a hiatus that could develop, during which Connaught would be unable to produce either non-heat-treated concentrate (the last of the Red Cross plasma having been processed) or heat-treated concentrate (the licence for the new product not yet having been received). On 10 January 1985, representatives of Connaught met with the executive committee of the Canadian Blood Committee. They explained that during any such hiatus Connaught would have no revenue from fractionating fresh frozen plasma and, unless steps could be taken to avoid such a consequence, Connaught would have to dismantle its production team. As a preventive measure, Connaught proposed that the committee provide it with temporary financial assistance to keep the production team in place. That proposal was reported to, and approved by, the full committee when it met on 15–16 January 1985. The committee instructed the Red Cross to negotiate the amount of the financial assistance with Connaught and to choose two of its own members, from Nova Scotia and Ontario, to be present at the negotiations. The committee eventually approved financial assistance for eleven months at \$124,000 per month, to be paid to Connaught by the Red Cross from its fractionation account. This was the account in which the Red Cross held provincial money in trust for the payment of fractionation-related expenses.

Two steps had to be taken before Connaught could make heat-treated factor VIII concentrate. First, it had to produce a high purity concentrate – that is, a concentrate that contained a high ratio of factor VIII to other plasma proteins. This step was necessary because there would be a significant loss

in factor VIII activity if large amounts of other plasma proteins were present during the heat treatment. Second, it had to refine the heat-treatment process itself so as to minimize any loss in factor VIII activity. Connaught had been working on the first of these steps since 1982. During 1984 it developed a process in which it added fumed silica to remove undesired proteins from the plasma, and then removed the silica before completing the processing. Connaught applied to the Bureau of Biologics for approval of the high purity factor VIII concentrate resulting from this process in the autumn of 1984, but on 17 December was told that the amount of silica left in the finished concentrate was unacceptably high.

Connaught increased its efforts to develop heat-treated concentrates after the consensus conference in December 1984. Nevertheless, it did not meet its target, to have a licence for heat-treated factor VIII concentrate by July 1985. First, approximately three months passed before it improved its process to reduce the silica levels in the finished concentrate to an acceptable level. Then the Bureau of Biologics, reversing an initial position, insisted that Connaught conduct clinical trials for its heat-treated concentrate, and the trials took another three months. Connaught finally secured a licence for its heat-treated factor VIII concentrate on 2 January 1986.

A few days earlier, a new issue had arisen that had a significant impact on Connaught's continued production of fractionated blood products. The Red Cross's liability insurance expired and was not renewed. Under its contract for custom fractionation, the Red Cross was required to indemnify Connaught for any liability resulting from the quality of the plasma it supplied. Connaught was unwilling to take the chance that an uninsured Red Cross would have the financial resources to honour that agreement should the risk of liability accrue. It initially refused to deliver any fractionated blood products to the Red Cross until the issue was resolved, but eventually relented and produced factor VIII and IX concentrates for the Red Cross from late 1986 to 1988. On 3 February 1986, the Red Cross and Connaught wrote a joint letter to the Canadian Blood Committee, asking it to solve the problem in one of three ways: by proposing legislation to limit liability, by allowing both the Red Cross and Connaught to self-insure (and to increase the price of fractionated products to the provinces to create the necessary funds), or by government guarantees to pay uninsured liabilities. The problem was discussed during the next year on five occasions by the full committee and its executive committee. In January 1987, the committee informed the Red Cross that

the CBC [Canadian Blood Committee] will support all reasonable costs associated with fractionation contracts which are necessary for the CRCS [Canadian Red Cross Society] to carry out its commitment to supply blood fractions from Canadian source plasma to the provinces and territories, as long as the CBC has specifically authorized the CRCS to enter into each particular contract and is aware of its provisions.

This proposal was not a satisfactory resolution of the issue. The committee did not directly say that the provinces would pay uninsured liabilities if necessary. Nor did it answer that question indirectly by including indemnification as one of the "reasonable costs associated with fractionation contracts." In May 1987, Connaught proposed to the committee that its custom-fractionation contract with the Red Cross be amended to incorporate in the cost of processing plasma "all costs incurred by Connaught in connection with any litigation or threatened litigation arising from the use of any plasma product prepared by Connaught from plasma supplied by the Red Cross." The committee agreed to support "a negotiated settlement" of the issue by Connaught and the Red Cross, subject to its approval of any settlement reached. However, events overtook the attempt to reach a settlement.

Throughout the 1980s, Connaught had never completely abandoned the possibility of building a new fractionation plant. The province of Ontario was willing to help it do so, and, in April 1987, gave Connaught \$6 million for this purpose. On 23 June 1987, Connaught announced that it was leaving the fractionation business and returned the money. There were four reasons for its decision: new technology was being developed for the production of recombinant, or genetically engineered, blood products, which would likely make a traditional fractionation plant such as Connaught's obsolete; the insurance and indemnification issue was still unresolved; a long-term agreement had still not been reached with the Red Cross for the supply of fresh frozen plasma and the distribution of products; and it had grown weary of dealing with issues through the cumbersome structure of the Canadian blood system. Connaught subsequently asked the Canadian Blood Committee to pay certain costs incurred in closing its fractionation business. At a meeting on 9–10 February 1988, the committee agreed to pay approximately \$2 million for that purpose.

The Winnipeg Rh Institute

At their meeting in December 1980, the provincial ministers of health agreed that the Rh Institute in Winnipeg should build a fractionation plant capable of processing 50,000 litres of Canadian plasma per year and that it should receive 25 per cent of all Canadian plasma for processing in its plant. Fifty per cent of the capital and development costs of the plant were to be paid by the province of Manitoba. The other 50 per cent were to be paid from revenues generated by the sale of products made in the plant. The products would be purchased by the provinces, which would pay according to the quantity of the products they used. In 1983, Manitoba's share of the development costs was reduced to 25 per cent. Three-quarters of the development costs, and 100 per cent of the operating costs, were now expected to come from the sale of products.

The technology that the Rh Institute proposed to use in its plant was new and unproven. The construction of the fractionation plant was completed by October 1983. By March 1984, the plant was expected to become operational by January 1985. On 15 November 1984, the Canadian Blood Committee was told that the plant would not become operational until 1 July 1985.

On 16 November 1984, the Bureau of Biologics issued its directive for the conversion to heat-treated factor concentrate. At the consensus conference on 10 December, a representative of the Rh Institute said that the new requirement was not expected to delay the licensing of the institute's factor VIII concentrate beyond the previously stated target of the following July. However, on 1 April 1985 the executive director of the Rh Institute reported to its board that "the commissioning of the Rh Laboratory fractionation process has continued to be plagued with mechanical problems"; he estimated that its factor concentrates would be licensed in August or September 1985.

In November 1985, the Rh Institute asked the Canadian Blood Committee for financial assistance similar to that which was being given to Connaught during its transition to heat-treated concentrate. The financial assistance was intended to pay unexpected expenses that had been incurred by the need to produce heat-treated concentrate and the consequent delay in licensing. The estimated amount involved rose during the next year from approximately \$1 million (8 November 1985) to approximately \$2.7 million (2 October 1986). More than \$1 million of the larger sum was interest on outstanding loans. The committee approved financial assistance at a meeting held on 2–3 November 1986, but only of \$1,040,548, for the period 1 July 1985 to 31 May 1986. All requests for the payment of interest were rejected. The committee told the Rh Institute that, if the institute was not licensed to produce factor VIII concentrate by 1 April 1987, the committee would reconsider its commitment to support further development costs.

The day before that deadline, on 31 March 1987, the fractionation operation of the Rh Institute was incorporated as the Winnipeg Plasma Laboratory. Nine days later, the Winnipeg Plasma Laboratory asked the Canadian Blood Committee for a one-year extension of the deadline, to 1 April 1988. The committee allowed the extension when it met on 1–2 September 1987.

Three months later, on 15 December, following the implication of dry heat-treated concentrates in the HIV infection of hemophiliacs, the Bureau of Biologics issued a new directive that such concentrates be replaced as soon as possible with factor VIII concentrate that had been produced by the safer wet or vapour heat-treatment processes. The process being developed at the Winnipeg Plasma Laboratory used dry heat treatment. The Bureau of Biologics told the Canadian Blood Committee that it would not license the Winnipeg Plasma Laboratory's dry heat-treated factor concentrate unless the supply of wet heat-treated concentrate proved insufficient. At a meeting on 9–10 February 1988, the committee then decided that it would provide no capital and development funding beyond the end of March. It also decided

that the payment of its share of capital and development costs, which was contingent on the Winnipeg Plasma Laboratory obtaining a licence for factor VIII concentrate, would be made only if regulatory requirements were met. Those requirements would be met only if the Bureau of Biologics issued the licence, or (if the bureau declined to issue any new licence for dry heat-treated concentrates) if the bureau confirmed that all regulatory requirements for dry heat-treated factor VIII concentrate had been met.

On 7 September 1988, the Bureau of Biologics issued a licence for the Winnipeg Plasma Laboratory's dry heat-treated factor VIII concentrate. But the concentrate could not be distributed because of the bureau's directive of 15 December 1987.

The Winnipeg Plasma Laboratory had, since early 1988, been making albumin from stored plasma supplied by the Red Cross, and had financed its operating costs through the sales of the albumin to the Red Cross. On 28 September 1988, the Canadian Blood Committee agreed to continue to finance the Winnipeg Plasma Laboratory's operating costs through albumin sales until at least February 1989. Because albumin was the only blood product produced by the Winnipeg Plasma Laboratory, all operating costs were allocated to it and its price, as a result, was approximately ten times the commercial rate.

In September 1988, the ministers of health of the provinces and territories, after considering a study on domestic plasma fractionation that had been prepared for them, requested proposals for the construction of a plant capable of fractionating 300,000 litres of plasma per year. The Winnipeg Plasma Laboratory tendered a proposal to build that plant. In 1989, it and all other proposals tendered were rejected. Decisions about developing a new fractionation plant were postponed pending the creation of the Canadian Blood Agency in 1991.

At a meeting on 4–5 October 1989, the Canadian Blood Committee decided to give the Winnipeg Plasma Laboratory \$250,000 per month until September 1990, to allow it time to "examine the options for the future."

In the end, no licensed factor concentrate that could be distributed was ever produced by the Rh Institute or the Winnipeg Plasma Laboratory. The amount of public money spent on the development of the plant and its products was approximately \$28 million. Of that, approximately \$5 million was paid directly by the province of Manitoba. The remainder was paid by all provinces through the Canadian Blood Committee.

The Institut Armand-Frappier

At their meeting in December 1980, the provincial ministers of health also agreed that the Institut Armand-Frappier in Laval, Quebec, should build a fractionation plant capable of processing 50,000 litres of Canadian plasma per year and that it should receive 25 per cent of all Canadian plasma for processing in its plant. From time to time throughout 1980 to 1988, representatives of Armand-Frappier made various predictions about the construction

of a fractionation plant. In June 1982, the Canadian Blood Committee was told that the construction of a plant would be completed by the spring of 1983. In June 1983, the committee was told that the plant would be completed and producing blood products by the end of 1984. In April 1984, the committee's advisory subcommittee was told that the completion of the plant was expected in December 1984 and that production would begin in the summer or autumn of 1985. In December 1984, the consensus conference was told that the plant would not be completed until 1986 at the earliest. In April 1985, the advisory subcommittee was told that the construction of the plant would begin in the autumn of 1986. In October 1985, the committee's executive committee was told that the construction would begin in the spring of 1986, subject to approval of financing by the province of Quebec. In November 1986 and October 1987, the advisory subcommittee was told that the approval of provincial funding was still pending. Construction of the plant was never begun.

Armand-Frappier also tendered a proposal to build the 300,000-litre fractionation plant approved by the provincial ministers of health in September 1988. Like all others, its proposal was rejected.

On 1 May 1990, Quebec's representative on the Canadian Blood Committee asked whether the committee would be willing to pay its share of capital and development costs related to Armand-Frappier's "fractionation activities," saying that a claim of \$6.2 million was possible, of which \$4.5 million would be for interest payments. The committee asked the representative to consider making a formal request. A formal request was made on 11 September 1990. It was rejected when the committee met in November 1990 because Armand-Frappier had not obtained a licence for factor VIII concentrate from the Bureau of Biologics, which was a condition of payment.

Consequences

In 1988, when Connaught closed its fractionation plant, Canada was left without a domestic source for any part of its demand for factor concentrates. As a result, for the past decade, all factor concentrates, and almost all other blood products, used in Canada have been made by foreign fractionators.

Treatment of Hemophiliacs in the Era of AIDS

When opportunistic infections were first reported in three hemophiliacs in the United States in July 1982, it was suspected that they were caused by a blood-borne virus. Many hemophiliacs rely on blood products to protect them from potentially disabling and life-threatening hemorrhages. Until the suspicion could be confirmed or denied, it was therefore important that the health of hemophiliacs be watched closely and that, as knowledge of AIDS grew, steps be taken promptly to minimize the risk of its transmission through the use of blood products. Measures were available to reduce the exposure of hemophiliacs to that risk. This chapter describes the steps that were taken by the Canadian Hemophilia Society, the lay organization that speaks on behalf of hemophiliacs, and the physicians and clinics that were treating hemophiliacs during the 1980s to tell hemophiliacs about the risk of infection and the means to reduce that risk. It also examines the way in which hemophiliacs came to learn whether they were infected with the human immunodeficiency virus (HIV), the agent causing AIDS, and the counselling associated with that notification.

The response of the National Hemophilia Foundation, the U.S. counterpart of the Canadian Hemophilia Society, and of the U.S. public health authorities to the report of the three hemophiliacs with opportunistic infections was immediate. The foundation issued a "patient alert" on 14 July, which was printed in the bulletins of its local chapters and circulated to U.S. hemophiliacs, health professionals, and other interested parties. The foundation issued "chapter advisories" and "medical bulletins" (distributed to "all providers who treat patients with hemophilia") as new information about the relationship between AIDS and hemophilia became available. Between July 1982 and December 1985, it issued thirty-two medical bulletins to physicians and thirty-seven notices to the presidents of local chapters. The Canadian Hemophilia Society, in contrast, relied on its quarterly publication, *Hemophilia Today*, to communicate new information about AIDS to its members. A discussion of the initial response of the Canadian Hemophilia Society and its medical and scientific advisory committee to the evidence of risk to hemophiliacs can be found in Chapter 10.

The development of recommendations to minimize the risk to Canadian hemophiliacs: January–March 1983

On the morning of 14 January 1983, Dr Hanna Strawczynski, the chair of the medical and scientific advisory committee of the Canadian Hemophilia Society, attended a special meeting of the medical and scientific advisory council of the U.S. National Hemophilia Foundation. The advisory council had drafted a set of recommendations for U.S. physicians treating hemophiliacs, commercial fractionators, and blood and plasma collection centres on ways "to prevent AIDS in patients with hemophilia." In the afternoon, she attended a second meeting at which these recommendations were discussed with senior representatives of the U.S. blood collecting and distributing organizations, manufacturers of blood products, and concerned government agencies, including the Centers for Disease Control and the Office of Biologics, the U.S. regulator. Dr John Derrick, the adviser on regulatory affairs and good manufacturing practice of the Canadian Red Cross Society (Red Cross), also attended the afternoon meeting on 14 January. During the meeting, Dr Christos Tsoukas, a Canadian immunologist, presented the data from a study he was conducting into the occurrence of immune dysfunction in asymptomatic hemophiliacs in Montreal. The study found that a substantial portion of a typical sample of asymptomatic severe type A hemophiliacs showed immune deficiency, a condition similar to that seen in persons diagnosed with AIDS.

The advisory council recommended that cryoprecipitate rather than factor concentrates be used in treating type A hemophilia in newborn infants and children under four, newly identified patients who had never been treated with factor VIII concentrate, and patients with mild hemophilia who required only infrequent treatment. Similarly, the use of fresh frozen plasma rather than factor IX concentrate was recommended for the treatment of type B hemophiliacs who had never or rarely been treated with factor concentrates. The council did not make specific recommendations for treating severe hemophilia patients, but said it would continue to review the data. The use of DDAVP, a synthetic drug that can increase the level of factor VIII, was also recommended for treating mild and moderate type A hemophiliacs. (DDAVP is ineffective in patients with less than 5 per cent of the normal level of factor VIII, and was not, therefore, useful in treating severe hemophiliacs.) To decrease the risk of infection, physicians treating hemophiliacs were encouraged to consider delaying elective surgery. Recommendations, described in Chapter 14 of this Report, were also directed to the manufacturers of factor concentrates and to regional and community blood centres. The National Hemophilia Foundation distributed the advisory council's recommendations to U.S. hemophiliacs and their physicians by way of a chapter advisory and a medical bulletin dated 17 January 1983.

On 24 January, Dr Strawczynski wrote to members of the medical and scientific advisory committee of the Canadian Hemophilia Society, saying that the epidemiology of AIDS was strongly suggestive of a blood-borne virus, that the reason why there were fewer cases of AIDS in Canada than in the United States could be related to the sizes of the populations, and that Canadian physicians treating hemophiliacs should expect to see cases of AIDS among their patients. She proposed an extraordinary meeting of the committee on 7 February 1983, to be followed on the same day by a meeting with representatives of the Red Cross blood transfusion service. She enclosed a copy of the recommendations issued by the medical and scientific advisory council of the National Hemophilia Foundation in her letter to the committee members.

On the morning of 7 February, the medical and scientific advisory committee drafted a series of recommendations designed to reduce the risk of infection with AIDS in the treatment of hemophilia. These recommendations were addressed to physicians treating hemophiliacs, the Red Cross, and the Canadian Blood Committee, the organization through which the provinces funded the blood system. The recommendations were presented to a meeting in the afternoon attended by the directors of most Canadian hemophilia clinics, members of the Canadian Hemophilia Society executive, senior representatives of the Red Cross blood transfusion service, and representatives of the federal Health Protection Branch. The participants agreed unanimously that the Canadian Hemophilia Society should draft a statement on their behalf "to be released to the press" and that "patients should not be alarmed unnecessarily." The press release issued by the society the next day included the following statement:

Canadian hemophiliacs can be assured of the fact that this situation will be closely monitored, and that there is no need at this moment for any hemophiliac to consider any major changes, either in method of treatment or lifestyle, unless so advised by his treating physician.

Although the advisory committee did not then know it, by this time half, if not more, of Canadian severe hemophiliacs were already infected with HIV.

The medical and scientific advisory committee of the Canadian Hemophilia Society formally issued its "Recommendations to Lessen the Risk of Exposure to AIDS in Patients with Hemophilia" on 3 March 1983. They were sent to all members of the society's medical and scientific advisory committee and executive, the directors of Canadian hemophilia clinics, and officials of the national office of the blood transfusion service of the Red Cross, the Bureau of Biologics (the Canadian regulator), and the Laboratory Centre for Disease Control (which conducted disease surveillance on behalf of the Government of Canada). The treatment-related portion of the recommendations was

communicated to Canadian hemophiliacs and their treating physicians through *Hemophilia Today*, and to Canadian physicians generally through the *Canada Diseases Weekly Report* of 26 March 1983.

The preamble to the recommendations said that no confirmed cases of AIDS had yet been reported among Canadian hemophiliacs, but that "[w]hile the agent causing AIDS remains unknown, there is some evidence that it may be transmitted through blood products." It continued: "It appears from [various] reports that patients using cryoprecipitate may be at a lesser risk of developing AIDS than those using concentrates."

The recommendations were modelled on those issued by the medical and scientific advisory council of the National Hemophilia Foundation in January. Those addressed to the Red Cross and the Canadian Blood Committee are described in Chapter 14. The recommendations for physicians treating patients with hemophilia read as follows:

- A) It is recommended that cryoprecipitate be used to treat those patients with classical hemophilia who have never previously received lyophilized concentrates. This group includes all newly diagnosed patients regardless of age and severity of hemophilia, and any patient who, for a variety of reasons, has been treated mainly with cryoprecipitate.
- B) Patients who belong to the above group and who, for medical or other reasons (travel, unavailability of cryoprecipitates, etc.) have to receive the lyophilized material, should be treated with Factor VIII concentrates of Canadian plasma origin whenever possible.
- C) All newly diagnosed and all mild cases of Factor IX deficiency should be treated with frozen plasma whenever possible.
- D) The [medical and scientific advisory committee] is cognizant of the fact that for most patients, lyophilized concentrates will still be the only feasible therapeutic modality, and urges all professionals involved in the management of hemophiliacs to reinforce the following:
 - 1 When appropriate, replacement therapy should be accompanied by conservative measures such as immobilization and splinting, in order to achieve the best results and to avoid large doses and prolonged treatment.
 - 2 Bleedings should be treated early in order to prevent severe hemorrhages that require high dose, prolonged treatment.
 - 3 Replacement therapy is not a solution for arthritic pain.
 - 4 For most of the bleedings treated at home, moderate doses are sufficient to ensure hemostasis.
- E) DDAVP should be used whenever possible in patients with mild and moderate classical hemophilia and in patients with mild and moderate Von Willebrand's Disease.
- F) All elective surgical procedures should be postponed until more information is available about the modes of transmission of AIDS.

Lyophilized (freeze-dried) factor concentrates were made from pools that contained the plasma of thousands of donors, any one of whom might be infected with the organism causing AIDS. A single contaminated donation could contaminate an entire pool. A unit of cryoprecipitate, in contrast, was derived from the plasma of single donors. Although treating a bleeding episode with cryoprecipitate required on average between three and four units, the risk of exposure to AIDS was thousands of times lower from cryoprecipitate than from factor concentrates. Approximately half the lyophilized factor VIII concentrate used in Canada, moreover, was manufactured by U.S. fractionators from plasma collected from paid donors, who were believed to carry a greater risk of infection than unpaid donors. The recommendations to physicians were intended to reduce therapeutic reliance on factor concentrates, particularly those produced from U.S. plasma.

The recommendations involved only modest changes in treatment. In the spring of 1983, in the Annual Report of the Canadian Hemophilia Society, Dr Strawczynski told Canadian hemophiliacs that "no major changes in the current treatment are being advised at the moment." She also stated that "[t]he agent causing the condition [AIDS] is still not known, and there is still no proof that it is transmitted by blood products." She testified:

We knew very little about AIDS, but we knew a lot about hemophilia and about the complications of bleeding. And at that time we just did not hear that there [was] a reason to go any further than [what] we proposed in our recommendations.

The implementation of the Canadian Hemophilia Society's recommendations

The physicians who treated hemophiliacs interpreted the advisory committee's recommendations in different ways. One testified that most physicians believed that the committee had recommended that they postpone elective surgery and avoid factor concentrates when treating soft tissue bleeding episodes, but that they should continue to use early infusions of factor concentrate in treating bleeding into joints. Another physician testified that he viewed the recommendations as a "restraint document" to temper the previous enthusiasm for using factor concentrates.

The recommendations did not have a substantial effect on the treatment of most hemophiliacs. Physicians treating hemophiliacs knew that immediate treatment of a bleeding episode with factor concentrate reduced the probability of morbidity and early death. Many did not recommend any change in treatment for their patients because they feared the patients might not treat themselves appropriately with factor concentrates when a bleeding episode began. Other physicians believed that their severely affected patients had already been exposed to the agent causing AIDS, and that returning them to cryoprecipitate would make no difference. Several physicians advised

the parents of younger patients to use cryoprecipitate. This response was little different from the then current practice in some regions where patients were kept on cryoprecipitate as long as feasible because of the greater risk of infection with hepatitis inherent in the use of factor concentrates.

For other physicians, however, an emphasis on cryoprecipitate was a substantial change in treatment; they ordinarily prescribed factor concentrate in newly diagnosed cases of severe type A hemophilia because patients could treat themselves at home. The tendency of treating physicians to prescribe factor concentrate rather than cryoprecipitate, because of its convenience, might have hindered the adoption of the recommendations by some physicians. The fact that DDAVP was not authorized for sale in Canada until April 1985 made it difficult to follow the recommendations strictly. The drug was initially obtained by some physicians through the emergency drug release program, and it was eventually approved for distribution at the urging of several treating physicians.

The first annual meeting of the Canadian Hemophilia Society after the release of the recommendations was on 14–15 May 1983. As was the custom, the medical and scientific advisory committee held its annual meeting a day earlier, on 13 May. It began with an open session, attended by many members of the society and devoted largely to AIDS. The first speaker was Dr Louis M. Aledort, the medical co-director of the U.S. National Hemophilia Foundation. He stated, as set out in the minutes:

It is still debatable whether AIDS is transmissible and, if it is transmissible, what is the real relationship to transfusion. Transfusion has always been a therapy with some potential risks. In relationship to hemophilia, the proven benefits still outweigh the proven risks. Dr Aledort indicated that his advice to his U.S. program is not to change treatment philosophy ("business as usual"). He did not think that NHF [National Hemophilia Foundation] guidelines issued in January 1983 represented a radical change in treatment policy.

In a closed session after the open meeting, the members of the medical and scientific advisory committee were less optimistic. The consensus of that meeting, as recorded in the minutes, was that "[d]espite Dr Aledort's reassurances ... caution was still needed. It was felt that denial was as inappropriate as the extreme emotionalism of the media." The minutes record that "[t]his message would be delivered by [Dr Strawczynski] to the National CHS [Canadian Hemophilia Society]."

The minutes of the advisory committee's open session on 13 May also reported that, except in Ontario, "the majority of patients had not changed their treatment philosophy because of AIDS." According to the minutes, the members of the Ontario chapter executive believed that many hemophiliacs were not receiving adequate treatment because they were afraid of contracting

AIDS. Two weeks earlier, that executive had asked the chapter's medical and scientific advisory committee to draft a statement about AIDS and the treatment of hemophilia as soon as possible for distribution to Ontario members because "[i]ndividuals either have stopped infusing any product or are using such reduced quantities as to be ineffective."

The Ontario chapter's advisory council held its annual meeting the next day, on 14 May. Dr Roslyn Herst, the chair of the council and the deputy medical director of the Red Cross blood centre in Toronto, had drafted a letter to Ontario hemophiliacs about AIDS and hemophilia and had circulated it to members of the council for their comments before the meeting. As recorded in the minutes of the Ontario advisory council meeting:

[C]hanges in immune parameters occur with cryo[precipitate] as well as lyophilized concentrate and appear to be related to dose rather than type of product. It was generally felt that there was no scientific justification to suggest switching from concentrate to cryo[precipitate]. Also, in the event that treatment was essential, the treatment should not be withheld because of concern for the plasma source of the product. The [national] guideline about elective surgery was not referred to in the Ontario letter as it was felt that the attending physician should be allowed to decide about expected benefits of surgery for a particular patient.

The text of Dr Herst's letter, as revised by the Ontario advisory council, diverged from the national advisory committee's recommendations. The national committee had recommended the use of cryoprecipitate rather than concentrates when feasible, encouraged a conservative treatment of bleeding episodes, and preferred concentrates made from plasma of Canadian origin. The Ontario advisory council's letter, however, recommended little change in procedures:

There is a great deal still to be learned about AIDS. Unfortunately, media coverage has been alarmist and somewhat distorted. Individuals with hemophilia should not hesitate to transfuse. Consideration should be given to the appropriate transfusion product for a particular individual. While the National MSAC [medical and scientific advisory committee] recommendations suggest that the use of cryoprecipitate or exclusive use of products from Canadian plasma reduces the risk of exposure to AIDS, the firm evidence for this is not available. Plasma source of product should not interfere with the decision to treat.

The Ontario advisory council concluded in its letter that "the risks of life-threatening or crippling bleeding episodes outweigh the potential risks associated with transfusion."

The advisory council's letter was distributed by the Ontario chapter to its members and to hemophilia clinics in Ontario, and by the Ontario Red Cross blood centres to hospital blood banks. It was also published in the June 1983 issue of the chapter's newsletter, *Hemophilia Ontario*.

The position of the Ontario medical and scientific advisory council was much closer to the Red Cross's position than that of the national committee. On 26 May 1983, Dr Roger Perrault, Dr John Derrick, and Dr Derek Naylor of the national office of the Red Cross blood transfusion service, which was located in Toronto, met with local public health officials to exchange information about measures that could be taken to reduce the risk of transmitting AIDS through blood. As recorded in the City of Toronto's memorandum of the meeting:

CRCBTS [Canadian Red Cross blood transfusion service] personnel emphasized blood and Factor VIII concentrates are very safe and hemophiliacs and other transfusion recipients need to be reassured of this. They thought the concentrates ... were safer than cryoprecipitate ... and both were far safer than unchecked bleeding from restrained use of Factor VIII. (They disagreed with the more conservative recommendations of the Canadian Hemophilia Society Medical and Scientific Advisory Committee which preferred cryo where possible). They were concerned about growing numbers of reports of hemophiliacs on self-treatment, who were not treating themselves.

On 6 September 1983, Dr Strawczynski sent a draft version of an article entitled "Update on AIDS" to all members of the national medical and scientific committee, proposing that, if they agreed, the text should be put in letter form and sent by the Canadian Hemophilia Society to its members. She said the letter was intended to alleviate some of the confusion and anxiety caused by the "sensational headlines" and "generally alarmist reports" in the media. In it, she emphasized the danger of not treating a bleeding episode, said that there was no proof that AIDS was transmitted in blood products, and that the medical and scientific advisory committee "still fully endorsed its recommendation of early 1983." She also said that factor concentrates made from the plasma of volunteer donors were not necessarily safer than those made from the plasma of paid donors. The letter appeared in the September 1983 edition of *Hemophilia Today*.

In the United States, the Hyland Therapeutics Division of Travenol Laboratories Inc. (Hyland), one of the four U.S. manufacturers of blood products, recalled in May 1983 factor concentrate lots made from pools containing plasma from a person subsequently diagnosed with AIDS. In response, the National Hemophilia Foundation issued a medical bulletin and chapter advisory that said that, because the risk was assessed as "very low" (twelve cases of AIDS out of 20,000 hemophilia patients in the United States), it recommended that

hemophiliacs continue using factor concentrates. Two other fractionators, the Cutter Biological Division of Miles Laboratories Inc. and Alpha Therapeutic Corporation, recalled factor concentrate lots for a similar reason in October 1983 and January 1984, respectively. On both occasions, the National Hemophilia Foundation issued an advisory in which it "reaffirm[ed] its recommendation that patients maintain the use of concentrate or cryoprecipitate as prescribed by their physicians."

The dilemma in choosing a form of treatment

Before the conversion to heat-treated factor concentrates, hemophiliacs and their physicians faced a dilemma in deciding the most appropriate form of treatment. On the one hand, the prompt use of factor concentrates to control a bleeding episode reduced the risk of physical disablement or death from bleeding. On the other hand, the use of factor concentrates increased the risk of contracting AIDS. Many patients and physicians had come to accept that there would always be risks associated with the use of blood products. Most hemophiliacs were already infected with hepatitis B as a result of factor therapy, but only a small percentage were known to suffer serious infection leading to liver failure or death. Some physicians believed that, as was true of hepatitis B, a hemophiliac exposed to the agent thought to cause AIDS could develop immunity to the disease. A further form of hepatitis – non-A, non-B (most of which is now classified as hepatitis C) – was becoming recognized and associated with factor therapy, but its risks were then little understood. Consequently, most hemophiliacs and their physicians believed that the benefits of treatment with factor concentrate far outweighed the associated risks of infection with hepatitis and, by extension, with AIDS.

In its recommendations of March 1983, the advisory committee had recognized that for most severe hemophiliacs requiring an extensive amount of clotting factor, factor concentrates were still the only feasible method of treatment to control a bleeding episode. For those patients who had a choice, the decision was not easy. Many patients were reluctant to surrender the convenience and therapeutic benefits of factor concentrates, which had revolutionized their lives, for the uncertain additional safety of cryoprecipitate. Dr Gershon Growe, the medical director of the Vancouver hemophilia clinic, testified about the implications of substituting cryoprecipitate for factor concentrates:

[Hemophiliacs] had become accustomed to a style of management of their life, and dealing with the supplementary product that they required for their health ... And it was very difficult to reverse this back to a status from five or ten years before ... We had a whole group of young men going to school. Boys playing sports. People getting educations and finding good employment ... In a short period of time, this really transformed the population of hemophilia patients themselves and their family lives. These

people were getting married, having children, considering things that they really hadn't done before even on cryo[precipitate]. They were also quite liberated in terms of their travel and their activities. And it was a very difficult step to consider abandoning that and moving back to something which seemed rather primitive in terms of treatment.

"They had 'just started to live,'" Dr Strawczynski testified, adding, "these are their words."

For many hemophiliacs, in short, a return to cryoprecipitate represented a significant retreat from a relatively normal life. Some physicians treating type A hemophiliacs recommended that their patients, including severe type A hemophiliacs, switch from factor VIII concentrate to cryoprecipitate for their factor replacement therapy. Some hemophiliacs did not follow this advice. Many others did not receive it. Those who did not belong to the Canadian Hemophilia Society or did not attend hemophilia treatment centres were unlikely to have been even aware of the society's recommendations.

Some hemophiliacs did modify their treatment. The amount of cryoprecipitate consumed nationally had declined by almost half in the three years since 1979, when the distribution of factor VIII concentrate free of charge began. This trend was reversed between 1982 and 1984, and consumption of cryoprecipitate rose by approximately one-third. However, the majority of persons with type A hemophilia continued to use factor VIII concentrate for routine therapy. The annual amount of factor VIII concentrate consumed nationally more than doubled from 1979 to 1982, and then remained almost constant until 1986, when it began to rise again.

Communicating the risk of infection with AIDS

To make an informed decision about the use of factor concentrates, hemophiliacs and their physicians needed to know about the risks associated with the use of those products. Some hemophiliacs had little or no medical supervision, and little or no contact with the Canadian Hemophilia Society. For them, the information contained in the product inserts that were part of the packaging of factor concentrates was particularly important.

Every vial of factor concentrate prescribed to a hemophiliac contained a printed insert describing the product, conditions for which it should be used, and, among other things, certain cautions related to its use. For example, the inserts packaged with the factor concentrates distributed in Canada contained a warning about the risk of acquiring hepatitis. The first factor concentrates distributed in Canada that contained information about the risk of AIDS were manufactured from plasma collected from paid donors in the United States. These commercial concentrates were distributed, beginning in early 1984, to every province except Nova Scotia, which received only custom-fractionated concentrates manufactured from Canadian plasma donated by

unpaid volunteers. It was not until the introduction of heat-treated products in mid-1985 that all factor concentrates distributed in Canada bore an AIDS warning.

Testing, notification, and counselling

All blood and plasma donations to the Red Cross were tested for the presence of HIV antibody by 1 November 1985. Alternative test sites were established in most provinces at the same time to allow persons who considered that they might have been exposed to HIV to test their status without going to the Red Cross to donate blood. For more than a year before that time, some testing was done at the Laboratory Centre for Disease Control in Ottawa. The availability of this service was announced in the *Canada Diseases Weekly Report* in August 1984, but few hemophiliacs were encouraged by their physicians to take advantage of the service, and some physicians testified that they were unaware of its existence. After the establishment of provincial test sites, testing became more common. Tests by the Laboratory Centre and the provincial laboratories were performed at the request of a physician, who was required to complete a detailed requisition form when sending a sample of blood. Most provinces did not ask for the name of the person being tested, but permitted the use of a code that prevented everyone except the attending physician from learning the patient's identity.

Dr Tsoukas began sending blood samples for HIV-antibody testing to the Laboratory Centre for Disease Control in Ottawa in the spring of 1984. Between 1984 and 1987, he coordinated a much larger study involving 372 participants from eleven centres in nine provinces. Blood samples were collected regularly from these patients, sent to Dr Tsoukas, and tested at the Laboratory Centre in Ottawa. Dr Tsoukas reported the results to the patients' physicians. At first, as many as ten months might elapse between the taking of the blood sample and the report to the physician. Although only one of the eleven centres was in Ontario, the directors of several other Ontario clinics also shipped samples to the Laboratory Centre, beginning in the spring of 1985, before provincial laboratory testing became available. In November 1984, a report of the early results from the Laboratory Centre showed that hemophiliacs had a high risk of exposure to HIV. More detailed information about the studies of HIV infection in hemophiliacs can be found in Chapter 26.

The physicians participating in the study were to communicate the test results to their patients. Several looked to Dr Tsoukas for advice. He testified that the results were difficult to explain to hemophiliacs because it was not known at first whether the presence of the antibody to HIV meant that the hemophiliac was infected or had developed a protective immunity.

Dr Tsoukas wrote to the directors of all the Canadian hemophilia clinics in March 1986, describing the guidelines he and his colleagues in Montreal had developed for notifying and counselling those of their hemophiliac patients who had tested HIV-antibody positive. "There is no easy way," he said, "to

tell the patients of their results." He explained the implications of infection with HIV and testing for its antibody as soon as one of his patients enrolled in the study or the next time he examined the patient, six months later. The patient was given the choice of being told or not being told the results of the HIV-antibody test. Many patients returned with questions about their condition. He explained that the test for HIV antibody was not a test for AIDS and "that the antibody screening has no relevance to their overall health but is important for public health reasons, i.e., safety of blood donations, limiting spread of this virus sexually, etc." Every effort was made to include the social worker and the nurse responsible for the patient in the discussion. Because testing was done as part of a research project, the results were not included in the patient's file.

In most hemophilia treatment centres, the nurse coordinator telephoned the patient when the test results were received and arranged an appointment with his physician. A survey of hemophilia treatment centres conducted in July 1985 found that, of seven in receipt of test results, only four reported the results immediately to their patients; the other three reported them only at the patient's request. The results were rarely reported by telephone, unless the patient lived a great distance from the clinic. If the patient was less than fifteen years old, his parents were usually told first. One physician testified that he followed Dr Tsoukas's suggestion and allowed the patient to decide whether to learn the test results; he said there was "relatively little advantage for most people to know," since there was then no known treatment for AIDS. A nurse at the clinic also counselled patients after they were informed of their test results.

The implications of HIV-antibody testing of hemophiliacs were extensively discussed at a meeting of the medical and scientific advisory committee of the Canadian Hemophilia Society on 1 November 1985. A major issue was that of patient confidentiality. At least one provincial laboratory was forwarding positive test results to the district health officer, and, as a result, a local hemophilia treatment centre decided to send its patients' blood samples to the Laboratory Centre for Disease Control because it reported test results only to the treatment centres. The committee recommended that hemophiliacs be told that their test results were confidential. More patients were asking to be tested, and these requests were placing increasing demands on clinic staff and resources. Counselling was discussed at length at the committee's next meeting, on 3 May 1986, where it was agreed that patients required individual counselling and that advice about safe sexual practices was particularly important. A fuller discussion of measures taken to reduce the risk of the transmission of AIDS from hemophilia to their sexual partners may be found in Chapter 21.

For many hemophiliacs, their hemophilia treatment centre was one of the few sources of information about AIDS, and the nurse coordinator was the primary contact there. Many nurses conducted workshops on AIDS in

conjunction with the local chapter of the Canadian Hemophilia Society. However, many mild and some moderate hemophiliacs did not attend a clinic on a regular basis, and some were completely unknown to either a clinic or the Canadian Hemophilia Society.

Commentary

By January 1983, there were clear indications that AIDS represented a significant, if unquantifiable and yet unproven, risk to the safety of hemophiliacs who used factor concentrates. It was prudent, therefore, to begin taking measures to reduce the risk and to monitor, and where appropriate modify, those measures as new evidence emerged.

Assessment and management of risk

Although not as quickly as its counterpart in the United States, the Canadian Hemophilia Society responded to the first published reports of AIDS among hemophiliacs. In March 1983, the society published its recommendations, drafted by its medical and scientific advisory committee, intended to lessen the risk of exposure to AIDS. These recommendations discouraged the use of factor concentrates by some hemophiliacs in favour of the safer cryoprecipitate. The advisory committee recognized that hemophiliacs who had never used concentrates were the least likely to have been exposed to the risk of contracting AIDS. To protect them, it recommended that, whenever possible, type A hemophilia patients who had never used concentrates or had been treated mainly with cryoprecipitate should be treated in the future with cryoprecipitate rather than factor VIII concentrate and that, whenever possible, newly diagnosed and mild type B hemophilia patients should be treated with frozen plasma rather than factor IX concentrate.

The committee underestimated the risk of contracting AIDS from blood and blood products in 1982 and 1983. Its members were not epidemiologists or virologists. By January 1983, however, the dominant theory about the cause of AIDS was that the agent was blood borne and infectious, and the syndrome had begun to appear among U.S. hemophiliacs with no risk factor other than their exposure to blood products. It was also common scientific knowledge that the latency period before the onset of symptoms was relatively long, that the mortality rate among persons diagnosed with AIDS was extremely high, and that a substantial portion of a typical sample of asymptomatic Canadian severe type A hemophiliacs showed immune dysfunction consistent with that found in persons diagnosed with AIDS. Furthermore, it was recognized that, if a biological agent is transmissible through blood products, the risk of infection is far greater in factor concentrates, which are manufactured from the pooled plasma of thousands of donors, than in cryoprecipitate, which usually is transfused from the plasma of no more than six individual donors.

The early statements from the medical and scientific advisory committee of the Canadian Hemophilia Society were reassuring. It is understandable that the physicians treating hemophiliacs should not want to alarm their patients, lest the patients stop treating themselves at the onset of bleeding episodes. However, the alternatives were not factor concentrate therapy as usual or no treatment at all. The advisory committee, and physicians in their individual practices, had the choice of a middle ground. The advisory committee could have extended its recommendations for the use of cryoprecipitate to at least occasional or infrequent users of factor concentrates, which would have included most patients suffering from mild and moderate forms of type A hemophilia. There was evidence that the Red Cross was able to increase its production of cryoprecipitate in response to an increased demand from treating physicians. There was no evidence that physicians were unable to prescribe cryoprecipitate for their patients because of a shortage of supply. The society's recommendations were not changed until the introduction of heat-treated factor concentrates in the summer of 1985.

Informing physicians and hemophiliacs about the risk of AIDS

Canadian physicians who specialized in the treatment of hemophiliacs had routine access to information about the risk of AIDS and the safety of blood products. This was not true of physicians in hospitals who might treat hemophiliacs on an occasional or emergency basis only. The Red Cross did not amend its *Clinical Guide to Transfusion*, first published in 1980 as "a source of current, basic information for clinicians about selected aspects of transfusion practice," to include information about the risk of transmitting AIDS through blood and blood products until 1987. Several directors of hospital blood banks and senior employees of the Red Cross testified that the clinical guide was the authoritative reference for determining appropriate indications for blood component and blood product use, and the risks associated with a blood transfusion. Several hematologists who taught medical students about blood transfusion practices testified that the guide was their principal resource, and that students were given copies of the guide to keep for future reference. To the extent that they consulted the guide throughout the early 1980s, physicians who had the need to order blood components or blood products would have relied on information that was silent about the risk of AIDS.

Some treating physicians who were fully apprised of the developing knowledge of AIDS adopted a paternalistic practice in conveying information about the risk of AIDS to their patients. They continued to reassure their patients about the use of factor concentrates rather than give them information that would allow them to make their own decisions about their care. Others were simply silent about the risk of AIDS and did not modify the treatment of their patients, despite the recommendations of the medical and scientific advisory committee to physicians to reduce the risk of exposure to HIV.

Labels warning about the risk of AIDS were added to the package inserts included with factor concentrates in the United States beginning in mid-1983; every vial manufactured for distribution in that country carried an AIDS warning by 1984. The Bureau of Biologics did not require similar warnings on the inserts for factor concentrates distributed in Canada at any time before the introduction of heat-treated products in mid-1985. Nor did the Red Cross, as the purchaser of these products, require the manufacturers to include an AIDS warning with their products. Labelling of this nature might have alerted general practitioners, emergency room physicians, and hemophiliacs, the ultimate users of the products, to the risk of contracting AIDS from factor concentrates.

For many hemophiliacs, the Canadian Hemophilia Society was an important source of information about the safety of the blood products on which they depended. This was especially the case for hemophiliacs who treated themselves at home, and who therefore did not regularly attend a hemophilia clinic. Despite its early promise to keep hemophiliacs informed through its quarterly publication, *Hemophilia Today*, as new developments emerged, the society did not provide timely information about AIDS. *Hemophilia Today* did not mention the first three cases of hemophiliacs with opportunistic infections in the United States until six months after the National Hemophilia Foundation had conveyed that information to its membership. Nor did the society adopt a means of communication more rapid than its quarterly newsletter, such as the frequent advisories distributed to local chapters by the U.S. foundation.

Testing, notification, and counselling

The announcement of the discovery of HIV in April 1984 confirmed that AIDS was caused by a virus that could be transmitted through blood. By July 1984, the Laboratory Centre for Disease Control was able to test for the antibody to HIV, and its ability to do so was announced in the *Canada Diseases Weekly Report* in August. Few hemophiliacs were told by their physicians about this early opportunity to be tested, or urged to undergo testing at the earliest possible opportunity. When hemophiliacs were tested, they were not always notified of their test results in a timely fashion. The risk of infection had serious implications, not only for hemophiliacs but also for their sexual partners and unborn children. It was important that hemophiliacs and their partners be tested promptly for the virus and told the results quickly, so they could be treated early when possible and advised about safe-sex practices.

The Public Health Authorities: Information about AIDS

In the efforts to control the spread of the emerging disease that came to be known as AIDS, information was an essential component. Public health officials and policy makers needed the most recent information about the nature and extent of the disease. They, in turn, had an opportunity to inform the public, and in particular the members of the public at the highest risk of infection, about the measures that could be taken to protect their own health and that of others. This information was particularly important before the summer and autumn of 1985, at which time two events occurred that substantially reduced the danger of the transmission of AIDS through the blood supply. These events were, first, the conversion to heat-treated factor concentrates and, second, the introduction of testing for the presence of HIV antibody and the screening of all blood donations for its presence. Even after 1985, however, the risk of transmission through blood and sexual contact remained, as did the importance of educating the public and high-risk groups about preventive measures.

Because the awareness of AIDS began outside Canada, and because most of the research about AIDS was conducted outside this country, Canadian public health officials were dependent on the international flow of information. Advances in the knowledge of AIDS were communicated through a number of channels. Research was published in such widely respected professional and scientific journals as *Nature*, *The Lancet*, the *Journal of the American Medical Association*, and the *Annals of Internal Medicine*, which were available and read in Canada. The natural history and spread of the disease were reported in *Morbidity and Mortality Weekly Report*, published by the U.S. Centers for Disease Control, and in its Canadian counterpart, *Canada Diseases Weekly Report*, published by the Laboratory Centre for Disease Control in Ottawa. Much information was communicated less formally through presentations at conferences and in conversations among experts. The Laboratory Centre for Disease Control collected and analysed information about the prevalence of the disease, but was hampered by the fact that reporting requirements varied among the provinces. As a result, not all physicians

were required to report cases of AIDS to the public health authorities in their respective provinces.

In May 1983, the federal government held a meeting of scientific experts in infectious diseases, drawn from Canadian universities, hospitals, and other organizations, to discuss the problems posed by AIDS. That group later became the National Advisory Committee on AIDS (NACAIDS). It was intended, in the words of the Minister of National Health and Welfare, Monique Bégin, "to provide a national resource base for information and coordinated activities through its interaction with provincial advisory committees and health departments as well as other AIDS study groups" and to give her "appropriate advice for the management of AIDS in Canada." The committee met irregularly, had limited resources, and, according to some of its members who testified, was primarily reactive. As a member of the committee said at the hearings: "We too often seemed to be trying to catch up or to follow ... And I would say that that was one of the weaknesses, and it was one of the frustrations that we felt, is that we always seemed to be responding to things. We never seemed to be in charge of it." The federal advisory committee did, however, prepare educational materials about AIDS, which it made available to provincial health authorities for them to reproduce or adapt for distribution to the public. One of these publications, issued in 1985, warned that the human immunodeficiency virus, or HIV, the causative agent of AIDS, was transmissible by blood, that hemophiliacs had contracted the disease through blood products, and that persons at risk of contracting AIDS should not donate blood. The list of persons at risk of contracting AIDS did not include the recipients of blood transfusions.

This chapter reviews the measures taken by the provincial public health authorities to obtain, exchange, and disseminate information about AIDS and the ways to control its spread through the blood supply.

Provincial advisory committees

In November 1983, Ms Bégin wrote to the provincial ministers of health, describing the role of the National Advisory Committee on AIDS and adding:

If you have not already done so, you may well find it advisable to authorize a similar committee within your province and it would be desirable if such a committee collaborated with the NACAIDS. If indeed such a group is formed or individuals are designated, I would be grateful if you would inform me in order that the National Advisory Committee may in turn be informed.

The Government of Ontario had already established a specialized committee of this nature in June 1983. No other provincial government responded to the federal Minister's suggestion in 1983, 1984, or the first few months of 1985.

In June 1985, a new Minister of National Health and Welfare, Jake Epp, repeated the suggestion in a letter to the provincial ministers of health:

Some provinces have found the development of a provincial advisory committee to be useful in communicating with the National Advisory Committee on AIDS. If you do not have such a committee, and AIDS is of concern and significance in your province, you may wish to consider such a coordinating mechanism.

I would hope that we can communicate further on this problem and that we are able to exchange further vital information as it arises.

The terms of reference of the Ontario Advisory Committee on AIDS were conducting research into AIDS; addressing the problems experienced by persons using blood products, particularly factor VIII concentrate; preparing information for health care workers; and assessing the needs for services such as treatment clinics and referral centres for infected persons. The committee was assisted by senior employees of the Ministry of Health, including the director of research, the director of the public health laboratory, and the physician manager of the disease control and epidemiology department. The Canadian Red Cross Society (Red Cross) was represented on the committee by Dr John Derrick, the adviser on regulatory affairs and good manufacturing practices, and in his absence by Dr Roger Perrault, the national director of the blood transfusion service; the committee depended on them to raise issues of concern with respect to AIDS and the blood supply and deferred to their expertise. In March 1984, the committee distributed publications about AIDS, which it had prepared, to physicians, hospitals, nurses, dentists, and medical laboratories. The publications, discussed later in this chapter, contained information about the transmission of AIDS through blood and blood products.

In some provinces, existing committees were aware of the transmission of AIDS through the blood system before a special committee on the subject was established. In Manitoba, for example, the subject was discussed in February 1983 at a meeting of the Cadham Provincial Laboratory-Preventive Medical Services (CPL-PMS) committee; the members heard the results of a study of abnormal immune response in hemophiliacs and examined the relative safety of cryoprecipitate and factor VIII concentrate. In June 1983, Dr Marlis Schroeder, the medical director of the Red Cross's Winnipeg blood centre, spoke to the committee about the transmission of AIDS and non-A, non-B hepatitis through blood and blood products and the death of a hemophiliac in British Columbia, apparently from contaminated factor VIII concentrate. In early 1985, the committee discussed the importance of tracing the recipients of contaminated blood components and of establishing a registry of AIDS cases in the province. Members of the committee, believing

that heat-treated factor VIII concentrate was available, recommended to the Ministry of Health that hemophiliacs no longer be treated with non-heat-treated concentrate. When the provincial government established an advisory committee on AIDS in June 1985, the director of the Cadham Provincial Laboratory, Dr Gregory Hammond, was selected as its chair. During the next two years the committee discussed, among other matters, the establishment of a provincial site for testing blood samples for HIV antibody, means of persuading persons at high risk of contracting AIDS to be tested at that site, and the dissemination of information to high-risk groups and the general public.

Some other provincial governments responded during the autumn of 1985 to the letter from Mr Epp by appointing expert committees (sometimes as a subcommittee of an existing body) to advise them about AIDS. The Government of Newfoundland established an advisory committee on AIDS in November 1985 in response to requests from local physicians treating hemophiliacs and from the Red Cross. The membership of the committee included the director of the Red Cross's blood centre in St John's, the director of the provincial public health medical services division, and the director of the public health laboratory. The committee discussed various issues related to the contamination of the blood supply with HIV, including the number of donors found to be HIV-antibody positive, the tracing of persons who had received HIV-contaminated blood, the significance of informed consent to testing, and the notification by public health authorities of the sexual partners of persons diagnosed as HIV infected. In British Columbia, the Minister of Health instructed the provincial medical advisory committee to form an advisory committee on AIDS in 1985, but the committee was not established until June 1987. In Nova Scotia and in New Brunswick, the governments continued to depend, for advice about AIDS, on its advisory committee on communicable diseases.

During the hearings in the provinces, public health officials gave various explanations for the late establishment of advisory committees. Some said that in the early 1980s there were no reported cases of AIDS in their province, or that the number of cases was not large enough to warrant a special committee. Others, like those in Newfoundland, believed that the need was being met by an existing committee. Some of these committees met infrequently, however. The advisory committee on communicable diseases in Nova Scotia, for example, met only two or three times in nine years, and its members lacked expertise in blood or blood products. Public health officials also referred to competing pressures. When asked why New Brunswick's community health advisory committee had not discussed the problems of AIDS before September 1986, the province's director of public health, who was also the chief medical officer of health, replied that there was always a considerable amount of work to do and "you want to do it at the time when you are going to be most effective."

Public health officials in some provinces testified that the advisory committees, whether designated for AIDS or for infectious diseases more generally, were not effective in shaping government policies with respect to AIDS and, in particular, to reducing the risk of AIDS to the blood supply. Most of the AIDS advisory committees were not created until after the period of greatest threat to the blood supply had ended with the introduction of heat-treated factor concentrates and the screening of donations for the presence of HIV antibody. The director of sexually transmitted disease control in British Columbia, who was the first chair of the provincial advisory committee on AIDS, said that the Minister of Health did not implement its recommendations and the committee did not receive responses to its proposals. Some provincial committees had no member knowledgeable about blood or blood products. On others, the only member with competence in these fields was a representative of the Red Cross, whose statements and opinion tended to be accepted without independent evaluation. In some provinces, the safety of blood and blood products was considered to be the function of the Red Cross and the Bureau of Biologics, and the committee focused on other AIDS-related matters. Blood and blood products were eliminated, for example, when new terms of reference were drafted for the advisory committee in Ontario in May 1984; the committee's chair testified that, at that time, an attempt was made to direct attention to matters that fell clearly within provincial jurisdiction.

Provincial-federal communication

There were two committees that could foster communication among federal and provincial public health officials. One was the National Advisory Committee on AIDS, which had been established in part to work with provincial advisory committees and health departments. The other was the Advisory Committee on Epidemiology, which had been established in 1962 as a forum for the regular consultation and coordination of federal and provincial public health officials and for the exchange of information about emerging infectious diseases.

The National Advisory Committee on AIDS had no provincial representation, and from 1983 to 1985, according to the chair of its epidemiology and public health subcommittee, no effort was made to coordinate its activities with provincial advisory committees. "The lack of linkage between NACAIDS and the provincial governments, as well as the lack of clear authority on the AIDS issues," were discussed at a meeting in June 1985 of the Canadian Blood Committee, the body through which the provinces funded the Red Cross blood transfusion service. Some members of the Canadian Blood Committee said that better coordination was needed because many issues, including public health and the financing of the blood system, fell within provincial jurisdiction.

The Advisory Committee on Epidemiology met only once a year. AIDS first appeared on its agenda in May 1983. At the hearings, Dr Alastair Clayton, the director general of the Laboratory Centre for Disease Control from 1979 to 1987, was asked why the committee did not discuss AIDS earlier. He replied:

In comparison with the other issues that were relevant in communicable diseases, it was not the biggest one. Now, that is not the best answer in the world, but it was certainly overshadowed by many other diseases.

AIDS was only one of many issues discussed by the committee. At its meeting in 1984, for example, the agenda contained twenty-six subjects, of which AIDS was one. Some federal officials, moreover, considered the National Advisory Committee on AIDS a more appropriate forum for the exchange of information about AIDS. The Advisory Committee on Epidemiology did not report directly to the deputy ministers of health but did so through the Federal-Provincial Advisory Committee on Community Health Services, which, when it met, also had many other matters on its agenda.

Some individual public health officials had regular contact with their federal counterparts. Others had little or no contact. Dr Timothy Johnstone, the director of the epidemiology division in the Ministry of Health of British Columbia, testified that he had discussions about two or three times a week with the members of the federal Bureau of Epidemiology on issues pertaining to AIDS. He also received statistics from the federal government of the number of AIDS-infected persons in Canada and distributed them to public health officials in British Columbia. Issues of the province's *Disease Surveillance* report were routinely sent to federal public health officials.

Representatives from the two levels of government met formally to discuss AIDS for the first time on 4 July 1985. The Red Cross was preparing to test blood donations for the presence of HIV antibody and it was important that the provinces establish their own test sites for the disease so that persons would not donate blood solely to learn their HIV status. In inviting the provinces to the meeting, the deputy minister of national health and welfare said: "Things are moving quickly and I consider it important that officials of federal and provincial governments get together in an attempt to establish a frame of reference within which to deal with the pressure caused by AIDS." Those attending the meeting included representatives of the Laboratory Centre for Disease Control and the Red Cross, the chair of the National Advisory Committee on AIDS, and, from the provinces, laboratory directors, epidemiologists, and other public health officials. British Columbia and Prince Edward Island did not send representatives, but senior public health officials in British Columbia arranged to be informed of the deliberations and decisions. At the meeting, the provincial representatives agreed to establish

alternative test sites that were universally available and easily accessible at no direct cost to the persons seeking the test, to provide counselling at the sites, to distribute material about AIDS to physicians, and to take measures to ensure the confidentiality of test results.

Shortly before the meeting on 4 July, the chief epidemiologist of Saskatchewan, Dr Roy West, complained in a departmental memorandum that decisions about testing for HIV had been made by the Red Cross, the Canadian Blood Committee, and the federal government, including the National Advisory Committee on AIDS, and that "[p]rovincial Public Health has not been involved in these decisions but is being asked to become responsible for the decisions." He said that the planned meeting on 4 July "in isolation cannot achieve in one day communications and discussions which should have been held over the last year. An ongoing work group needs to be established with representatives from all involved constituencies." Other public health officials complained after the meeting about the lack of federal-provincial communication. In September 1985, for example, Dr John Waters, the director of communicable disease and epidemiology of Alberta, wrote:

We are concerned with the lack of provincial input in planning for AIDS surveillance and management. Apart from the July 4, 1985 meeting, the Provinces have not been consulted and even information provided has been limited. Responsibility for managing AIDS and its related problems clearly lies with the Provinces and it is imperative we be involved with planning and not simply be presented with decisions and recommendations already made. We are also concerned with the lack of public health expertise amongst those developing plans and recommendations. It is essential that the Ad Hoc federal-provincial committee which met in July meet again regularly until a "steady state" is reached and that the responsibility for ongoing coordination and planning then be referred to a group such as the Advisory Committee on Epidemiology.

In Manitoba, Dr Hammond wrote in a similar vein to his deputy minister of health in October 1985. Complaints of this nature were not restricted to the western provinces. As early as March 1984, the Ontario Advisory Committee on AIDS believed, according to its minutes, that "very little had been done at the federal level and that there was little interest in coordinating with provincial activities at present," and at a meeting of provincial and territorial ministers of health on 25 September 1985, the ministers from Ontario, Prince Edward Island, Alberta, and New Brunswick said that federal collaboration with the provinces about AIDS was inadequate. The provincial ministers said that the federal government should coordinate AIDS-related public education and research throughout the country.

The deputy minister of national health and welfare, David Kirkwood, acknowledged these concerns in inviting the provinces to the second federal-provincial meeting on AIDS in December 1985. He said that better communication and coordination of strategies between the two levels of government was necessary to contain the spread of AIDS. At the December meeting, it was agreed that

- AIDS should be notifiable in each province and territory.
- Provincial and territorial departments and ministries of health would give the Laboratory Centre for Disease Control the data about AIDS and HIV infection needed for national surveillance, and the laboratory centre would send national statistics regularly to the provinces and territories.
- The national and local centres of the Red Cross blood transfusion service would report regularly to provincial and federal epidemiologists about the number of blood donations that were confirmed HIV-antibody reactive and the total number of units tested.
- The Laboratory Centre for Disease Control, in collaboration with non-governmental organizations, would compile an inventory of Canadian materials and persons who could be used in public education campaigns about AIDS, and would distribute it to provincial and territorial departments and ministries of health.
- Federal, provincial, and territorial representatives should meet regularly to discuss AIDS-related issues.

In August 1987, the Federal-Provincial/Territorial Advisory Committee on AIDS was established as a formal mechanism to facilitate cooperation between the two levels of government. The tasks of the committee included the development of a unified approach to AIDS, the establishment of national policies for controlling AIDS, and the coordination of federal, provincial, and territorial programs of education for public health workers and high-risk groups. The committee was to serve as a forum for the exchange of information, current research findings, and expert opinions and as a means of encouraging collaboration among governmental and non-governmental agencies and the private sector to promote a national approach to AIDS.

Interprovincial communication

In his testimony, Dr Peter Sarsfield, the director of the health and wellness branch of the Manitoba Department of Health, said that to respond rapidly and effectively to an epidemic, the smaller and less wealthy provinces must be able to draw on the expertise, research, and educational materials of the wealthier provinces. Dr Michael Bowmer, a professor of medicine at Memorial

University in Newfoundland, also testified to the need for a formal mechanism for communication among the provincial public health authorities. He said:

I think that HIV / AIDS has taught us an awful lot about many issues, all the way from informed consent and various risks to how we as a medical community respond to these diseases. You see balkanization throughout the system of researchers, of primary care physicians, of consultants, of public health officials ... There was not a mechanism at that point in time for the rapid transmission of information across the country. There was not a mechanism by which the literature that was being published by one organization was automatically flowing through another organization.

Public health officials in Ontario and British Columbia made efforts to exchange information during the emergence of AIDS. The educational materials developed for health care workers by the Ontario Advisory Committee on AIDS, along with issues of the *Ontario Disease Surveillance Report*, were sent to the Ministry of Health of British Columbia. The medical officer of health in Toronto also sent material about AIDS to health officials in British Columbia. Dr Johnstone sent copies of the British Columbia *Disease Surveillance* report and other material about AIDS to epidemiologists and public health officials in Ontario and in other provinces. There was little other exchange of information about AIDS among provincial public health officials before the introduction of testing for HIV antibody in November 1985, however, and it is uncertain how effective even the limited amount of interprovincial communication was. Senior public health officials of Alberta and Nova Scotia testified that they were not aware that a hemophiliac who had used factor concentrate had died from AIDS in British Columbia in March 1983.

In late 1985, public health officials grew increasingly aware of the importance of exchanging information about AIDS. In October, Dr Hammond wrote, in the same letter mentioned above to the deputy minister of health of Manitoba:

The other area in which your understanding and input would be very useful is in communications with colleagues of other provinces ... We need improved two-way communications, especially to avoid duplication of effort.

Medical officers of health from Victoria, Vancouver, Calgary, Edmonton, Saskatoon, Regina, and Winnipeg met in October 1985 and decided to arrange a meeting with representatives of the National Advisory Committee on AIDS and the medical officers of health from other Canadian cities where AIDS was prevalent. The first meeting of the Canadian Urban Medical Officers of Health took place on 26 February 1986. Some of the issues discussed were

contact tracing, the implications of proposals to close gay bath houses, and the occupational risks of acquiring AIDS. There was a consensus that the provinces should devote more funds to programs to prevent the spread of AIDS and that there was "an urgent need for research."

International communication

Public health officials in Ontario and British Columbia followed the development of AIDS in the United States throughout the 1980s in the belief that the Canadian experience would be similar. In the early years of the decade, public health officials from Ontario attended workshops sponsored by the National Institutes of Health, met with experts at the Centers for Disease Control, and communicated with public health officials in U.S. cities with a high incidence of AIDS. For example, beginning in 1983, the medical officer of health of Toronto and members of his staff had frequent discussions with officials in San Francisco with respect to public education about AIDS. Public health officials in British Columbia were in contact with officials at the Centers for Disease Control and maintained regular communication with state epidemiologists in Washington, Oregon, California, and, to a lesser extent, Alaska, Idaho, and Nevada.

Public health officials in all provinces received copies of the *Morbidity and Mortality Weekly Report*, published by the Centers for Disease Control. Their direct communication with U.S. public health officials about AIDS was at best minimal, however, before the introduction of HIV-antibody testing. Few attempts were made to obtain educational materials prepared in the United States or to learn about measures taken there to protect the blood supply.

Some provincial public health officials relied on the World Health Organization to obtain information on AIDS. The World Health Organization collected statistics of the number of AIDS-infected persons worldwide, formulated recommendations aimed at reducing the spread of AIDS to the blood supply, and developed public health measures to minimize the transmission of the virus. Its representatives visited health ministries of countries that sought advice about effective ways to contain this rapidly spreading communicable disease.

In 1982, the World Health Organization established a registry of diseases in Lyons, France, at the Edouard Herriot Hospital, and it sponsored a conference on immunodeficiency diseases at the University of Washington School of Medicine. One of its 1982–3 publications reported that the number of AIDS cases was increasing globally, that the disease appeared to be transmissible by blood and blood products, and that it had a high mortality rate.

Current studies of the disease were presented, and recommendations were made about epidemiology and surveillance, etiology, clinical diagnosis, and prevention and control of AIDS. Gay men were identified as a group at high risk of contracting AIDS, and it was suggested that public health

authorities contact gay groups for the purpose of developing measures to reduce the spread of the virus. Blood transfusion recipients and hemophiliacs who used factor concentrates were also described at risk of developing AIDS. The World Health Organization recommended that nations take the following measures:

- 1) Education of the general public and donor groups about AIDS.
- 2) Exclusion of blood donors who belonged to high-risk groups.
- 3) Avoidance of non-essential use of blood and blood products.
- 4) Preparation and use of blood and blood products in such a way as to reduce the risk of transmission of AIDS.

It suggested that public health officials inform physicians and persons with hemophilia of the risk of contracting AIDS through factor VIII and factor IX products, and that physicians be advised of the benefit of using autologous blood for suitable patients.

The World Health Organization reported that, as of 15 November 1983, there were fifty reported cases of AIDS in Canada, 44 per cent of which were in Montreal, Quebec. The epidemiological pattern of AIDS in Canada was considered similar to that in the United States.

In April 1985, the World Health Organization and the U.S. Department of Health and Human Services sponsored an international conference on AIDS. An issue of the World Health Organization *Bulletin* in 1985 discussed some of the information presented at the conference. It stated that since the emergence of AIDS in 1981, approximately 11,000 cases had been reported, most of which were in industrial countries. In North America, Europe, and Australia, gay men constituted 70 per cent of the AIDS cases. Others infected were hemophiliacs, blood transfusion recipients, intravenous drug abusers, and heterosexual partners and infants of persons at risk of infection. The *Bulletin* noted that the reported incidence of AIDS in Canada was increasing.

The World Health Organization stated that "the most promising means" of reducing the spread of AIDS was through education designed to modify behaviour. It recommended that information about the disease, including the routes of transmission and a description of measures to reduce the risk of AIDS, be widely distributed to the general public and to groups at risk of infection in language that would be easily understood by an average member of the public.

After the 1985 international conference, the World Health Organization established a network of collaborating centres on AIDS to promote international cooperation. Some of the services it made available were epidemiological surveillance, the provision of reagents, and the training of health care workers. In 1988, it established the Global Blood Safety Initiative to reduce the risk of HIV and other blood-borne pathogens such as hepatitis and Chagas' disease through blood and blood products. It developed guidelines for the

appropriate use of blood, established databases of country profiles, and conducted research. At the hearings, public health officials in British Columbia and Alberta testified that they used the resources of the World Health Organization in the 1980s to help contain the spread of AIDS in their respective provinces.

The Council of Europe, which was composed of twenty-one European countries, was another source from which provincial public health officials could obtain information on the transmission of AIDS. In June 1983, the council recommended methods to prevent the transmission of AIDS to hemophiliacs and to blood transfusion recipients. Nations were advised not to use coagulation factor products that had been prepared from large plasma pools. The Council of Europe also encouraged member states to strive to become self-sufficient in the production of blood products and to avoid the importation of blood products from countries where donors were paid. It recommended that prospective blood donors be provided with information about AIDS so that persons in high-risk groups would be deterred from making blood donations.

In September 1985, the Council of Europe made recommendations about HIV screening of blood donations. Member states were advised to establish alternative test sites before the introduction of HIV testing by the blood transfusion services in their respective countries. The purpose of these alternative test sites was to deter high-risk persons from donating blood solely to learn whether they were HIV positive. The council also recommended that counselling be made available to any person who had "abnormal serological findings" and that donors be informed that their blood was being tested for AIDS markers.

The 1987 Council of Europe recommendations were published under the title *A Common European Public Health Policy to Fight the Acquired Immuno-deficiency Syndrome*. They stated that the most effective method to reduce the spread of the AIDS virus was through preventive measures aimed at behavioural change. Member states were encouraged to take a united public health approach to AIDS at the national, regional, and local levels. The council recommended that member states establish AIDS committees at these three governmental levels to implement public health policies: "a regular flow of information and vertical and horizontal coordination ought to exist." It delineated the functions of these AIDS committees as prevention, through health information programs directed at both the general public and groups at risk, as well as through health promotion programs; public health regulatory measures; provision of health care services; training of staff; and research and evaluation.

In its 1988 recommendations, the Council of Europe stressed that transfusion was an important component of public health. It took the position that the blood transfusion services in the member states could be delegated to non-profit organizations, but that it was incumbent on health officials to supervise the activities of their blood programs.

Communication with the Red Cross

During the period when the blood supply was at the greatest risk of contamination with AIDS, before the Red Cross began screening donations for the presence of HIV antibody in November 1985, provincial authorities had opportunities to exchange information with Red Cross officials and to influence the Red Cross's policies about donor screening and education. Public health officials in Manitoba, British Columbia, and Ontario did exchange information about AIDS with the Red Cross during that period in informal contacts, through provincial committees, and at meetings convened by medical organizations. Research findings about AIDS and its precursor states, statistics of the prevalence and incidence of AIDS, and the measures that had been introduced in the United States to protect the blood supply were all discussed. In general, however, provincial authorities in those provinces deferred to the expertise of the Red Cross in matters of blood collection and safety, and did not attempt to influence or evaluate their policies.

In Manitoba, as we saw earlier, Dr Schroeder spoke in June 1983 at one of the weekly meetings of the Cadham Provincial Laboratory-Preventive Medical Services committee. The provincial epidemiologist, Dr J.A. Eadie, staff members of the laboratory, and some members of the University of Manitoba's Faculty of Medicine were present. Dr Schroeder reported an 88 per cent increase in the use of factor concentrates in Manitoba, and referred to the case of Artibano Milito, the hemophiliac in British Columbia who had died of AIDS. The committee members discussed the study on AIDS published by the U.S. National Institutes of Health, which showed that hemophiliacs, gay men, and Haitians were at risk of developing the virus. Dr Schroeder reported that Manitoba blood donors who had recently seen a physician were asked if they suffered from night sweats, weight loss, or swollen glands, all of which were possible indications of AIDS. The committee recommended that Dr Schroeder and Dr Eadie contact the leaders in the Manitoba gay community to discuss the means by which gay men could be deterred from donating blood. In 1987, Dr Schroeder reviewed educational materials about AIDS prepared by the province for physicians. Despite regular communication between the Red Cross and Manitoba public health officials, provincial officials did not attempt to influence Red Cross policies with respect to AIDS. Although some public health officials had doubts about the effectiveness of donor screening and about a lack of privacy at blood collection sites, their concerns were not conveyed to the Red Cross.

In Ontario, Dr Derrick, as a representative of the Red Cross, was a full member of the Ontario Advisory Committee on AIDS and was asked to report about issues related to AIDS and the blood supply. He was the only person on the committee with experience in blood and blood products and, as Dr Mary Fanning, the chair of the committee, testified, "there was no one on the committee who had expertise to support or challenge his views." She also testified that "[e]veryone ... took a hands-off approach to the issue of screening

high-risk donors as it was believed to be the responsibility of the Red Cross." When, in 1983, the Ministry of Health was considering whether to commission research into the safety of blood products, Dr Fanning reported to the assistant deputy minister for community health services that the Red Cross believed the study was unnecessary; she said that Dr Derrick had told the committee that "both the Red Cross and Federal and United States regulatory bodies were paying attention to this issue and that any efforts on our part in this area would be duplication." In March 1984, the committee distributed booklets about AIDS to physicians, nurses, dentists, hospitals, and medical laboratories in the province. Dr Derrick had been given the task of reviewing the portions dealing with the transmission of AIDS through blood and blood products. The booklet for physicians described the risk of contracting AIDS through blood or blood products as very small:

Although it is suspected that the agent responsible for the transmission of AIDS may be blood-borne, based on current evidence the possibility of developing AIDS after a blood transfusion is extremely low ... On the basis of 10 million blood transfusions during the last three years, chances of developing AIDS from a blood transfusion in the U.S. are about 1.5 in a million.

As demonstrated elsewhere in this Report, the calculation of risk was unrealistically low. The Red Cross did not at the time support an autologous blood transfusion program; the booklet did not recommend that physicians consider alternatives to donated blood or the postponement of elective or cosmetic surgery. The chair of the committee testified that the booklet was intended to reassure physicians that the risk of contracting the virus through blood and blood products was minimal. The close relationship of the advisory committee and the Red Cross was demonstrated in early July 1983, when the chair told members of the committee that an emergency meeting might be convened by Dr Perrault, the national director of the blood transfusion service, or his assistant, Dr Martin Davey, during the summer if the Red Cross experienced "urgent problems in availability of blood."

The City of Toronto's public health department also communicated with the Red Cross. In the spring of 1983, some members of its staff met with senior officials from the national office of the blood transfusion service – Dr Perrault, Dr Derrick, and Dr Derek Naylor, the director of blood products services – to learn what policies the Red Cross had adopted to reduce the risk of contamination of the blood supply, coordinate the two organizations' public announcements with respect to AIDS, and tell the Red Cross about measures taken by the city's public health department to control AIDS. At that meeting, the three officials from the Red Cross stated that the blood components and blood products used by Canadians were safe and that hemophiliacs and the recipients of blood transfusions should be assured

that the risk of AIDS was low. By this time, the Centers for Disease Control had reported several cases of AIDS among hemophiliacs, and a link was established between AIDS and blood products. When, in 1983, public health department officials prepared answers to questions about AIDS that they expected to be asked by the media, senior officials in the Red Cross blood transfusion service drafted the responses on the blood supply. In them, they said that there was no evidence that the blood supply in Canada or the United States was contaminated with AIDS-causing agents, and they advised patients not to cancel elective surgery "since at this time, there is no evidence that blood is any less safe than prior to the appearance of AIDS."

Dr Alexander Macpherson, the medical officer of health of Toronto from 1981 to 1988, testified that the Red Cross was preoccupied with maintaining a consistent supply of blood:

Our view was that the Red Cross should use donor questionnaires [that is, ask donors about their possible exposure to AIDS and the state of their health] although to control this was beyond our jurisdiction ... In general, we made our views known but that went into the decision-making process at the Red Cross. At that time ... the Red Cross, I believe, was very concerned about losing their donor pool. People at the time were connecting AIDS with blood donation and they were worried they would lose their donor pool.

It wasn't our role at that time to quarrel with anybody. We were liaising with the Red Cross.

We would have liked ... to see better donor screening earlier, but we considered that was the Red Cross's domain.

In British Columbia, representatives of the Red Cross were invited to attend meetings of provincial committees at which AIDS was discussed, and public health authorities and the Red Cross routinely exchanged information about infections attributed to blood and blood products. Here, too, the public health authorities deferred to the Red Cross's expertise. In January 1983, the director of the provincial division of epidemiology wrote to the assistant deputy minister to whom he reported that the medical director of the Red Cross's Vancouver blood centre did not support recent recommendations of the U.S. National Hemophilia Foundation designed to reduce contamination of the blood supply with AIDS. No efforts were made by provincial authorities to encourage the implementation of these recommendations, which included measures to have members of high-risk groups refrain from donating blood. In 1984, the British Columbia Ministry of Health received both the jury's verdict and recommendations and the coroner's comments from the Milito inquest. The jury recommended that the Red Cross take measures to ensure that factor VIII concentrate received from U.S. sources be "collected in such a manner that its use presents a minimal risk to Canadian

users"; "a further warning" be placed on "Factor VIII concentrate packages regarding the assumed danger of AIDS transmission"; and additional blood donor clinics be held "in the hope of collecting more plasma for refracting [sic] Factor VIII concentrate thereby decreasing the amount of imported Factor VIII." The Ministry of Health did not monitor whether these recommendations were implemented. The members of the Canadian Blood Committee were informed of the jury's verdict and recommendations and the coroner's comments in October 1984.

In the 1980s, public health officials in Nova Scotia met on a regular basis with officials of the Red Cross blood transfusion centre at the meetings of its provincial blood program committee. The committee included the medical director of the Red Cross's Halifax blood centre, the director and assistant director of blood donor recruitment for the Red Cross in Nova Scotia, representatives of the Department of Health, and members of the public. The principal interest of the committee, which normally met four times a year, was the recruitment of blood donors. At its meeting in January 1983, Dr Max Gorelick, the medical director of the Halifax blood centre, explained that AIDS could be transmitted, among other ways, by the transfusion of blood and blood products, that 800 persons in the United States were infected with the disease, and that 41 per cent of them had died. A representative of the Department of Health, the director of a health unit, said that the link between AIDS and blood transfusion was "extremely sketchy"; she and Dr Gorelick agreed that "to restrict blood donors at this time would be a fatal mistake." At later meetings, the Red Cross representatives said that the province might experience shortages of blood because of an erroneous public fear of contracting AIDS through donating and that "with the media blowing the AIDS issue way out of proportion, we must do all we can to allay the fears of donors." At a meeting in January 1986, the provincial director of community health services and the director of a local health unit expressed their "deep concerns" that the Red Cross was not doing enough to exclude donors at high risk of contracting AIDS. The director of community health services said that sexually active gay men had not received the Red Cross message and that they continued to donate blood at Red Cross clinics.

In other provinces, there was little effective communication between public health authorities and the Red Cross before the introduction of testing for HIV antibody. Senior public health officials in some provinces testified that they were unaware of press releases issued by the Red Cross in March and July 1983 asking AIDS-infected persons, sexual partners of those infected, sexually active homosexual or bisexual men with multiple partners, recent Haitian immigrants, drug abusers, and sexual partners of persons at high risk of contracting AIDS not to donate blood.

The lack of a coordinated approach to this disease by Saskatchewan health officials and the Red Cross is evident in a pamphlet distributed by the government to its employees a few months after the Red Cross press release of

March 1983. The provincial pamphlet encouraged its employees to donate blood and not to concern themselves with whether they were healthy blood donors. The brochure said: "At the blood donor clinic, you will be screened for any temporary or permanent health problem so you need not worry about being healthy enough to donate." As a senior public health official stated at the hearings, this pamphlet demonstrated a lack of communication between the Ministry of Health and the Red Cross.

In their testimony, some provincial public health officials said they believed that the safety of the blood supply was being monitored by the federal government; they were unaware that the Bureau of Biologics, although it did regulate blood products, did not regulate blood components or the collection of whole blood until 1989. Some said they did not work more closely with the Red Cross because they believed the risk of transmission of AIDS through the blood supply was low. A senior public health official in Nova Scotia said he relied on the calculation of one in a million to estimate the risk of contracting AIDS through a blood transfusion. Some provincial officials said they relied on the Red Cross to alert them to any public health problems that would arise from the new disease; as one said, "[w]e would respond and get directly involved only if problems came to our attention." Some testified they did not have adequate resources or the expertise to assess measures taken by the Red Cross to safeguard the blood supply; others said they considered the officials at the blood transfusion service to be well informed and "trusted" the Red Cross to take the necessary measures. Some said they found it difficult to influence the Red Cross. Others said they tried to focus their efforts in areas not under the Red Cross's authority.

Information for the general public

Provincial public health officials had an opportunity in the early 1980s to inform the general public about the ways in which AIDS was transmitted, the groups most at risk of infection, and measures that would reduce the risk of contracting or spreading AIDS. In 1983, three members of the public health department of the City of Toronto were asked to direct their effort towards an intensive educational campaign about AIDS. They prepared pamphlets, posters, and videotapes. The pamphlets, based on information in the *Canada Diseases Weekly Report* and the *Morbidity and Mortality Weekly Report*, explained that the virus was transmissible through sexual contact among homosexual men, shared needles used to inject drugs, blood products used by hemophiliacs, and blood transfusions. The pamphlets reinforced the message of the Red Cross that persons at high risk of contracting AIDS should not donate blood.

Before the introduction of HIV-antibody testing in November 1985, provincial and local public health officials, with few exceptions, did not take steps to inform the general public about AIDS and, in particular, AIDS in the blood

supply. They did not organize media campaigns, distribute pamphlets or other material about AIDS, or establish telephone information services that would enable the public to obtain information and advice anonymously.

Public education was important even after the introduction of testing for HIV antibody in November 1985, because persons already infected but not yet showing the indications of AIDS could infect their sexual partners unknowingly, and members of high-risk groups could still contaminate the blood supply by donating during the early period of infection when the antibody could not be detected. Moreover, persons who had been in any manner exposed to infection could discuss with their physicians the possibility of HIV-antibody testing at the provincial sites.

Some physicians, nurses, and other health care workers encouraged the public health authorities to address the issue of public education, but with little success. In British Columbia, for example, Dr Johnstone, the director of the epidemiology division of the Ministry of Health, recommended to his superiors in April 1983 that, in the absence of any government publication about AIDS, the Ministry of Health distribute copies of a pamphlet prepared by a community organization, AIDS Vancouver; his suggestion was rejected. Dr Brian Willoughby, a physician who treated AIDS-infected patients, wrote to the Minister of Health in May 1984 to say that the number of cases of AIDS in British Columbia was increasing rapidly and that it was important that public information be distributed to control the spread of the disease. Dr John Blatherwick, the medical officer of health in Vancouver, expressed a similar concern one year later in a letter to the deputy minister of health. The government did not distribute educational material until August 1985.

In September 1985, Professor Grace Getty of the University of New Brunswick's Faculty of Nursing, who had conducted research into the health of gay men in 1984 and 1985, urged the province's chief medical officer and director of public health services to distribute information about AIDS to the general public and to groups at high risk of infection. In October 1985, Dr John Hoey, a physician at the Montreal General Hospital, wrote to the epidemiologist who monitored AIDS for Quebec about the need for measures to curtail the spread of AIDS in the Montreal region and suggested that mass education programs be developed by the province for the public and for HIV-infected persons. He wrote: "I believe that we need to be desperately proactive in this area. We have the advantage of 2 to 3 years lead time on major United States cities. We can learn from their experiences and we may be able to limit the spread of this disease. I believe this is urgent and requires action in terms of the development of specific programs by early next year." Quebec did not organize an AIDS educational campaign for the public until 1987.

The information that was prepared was not always complete. For example, a brochure issued by public health authorities in British Columbia in August 1985, called *AIDS: How Not to Get It*, listed, as persons at risk of

contracting AIDS, gay and bisexual men who had "many different" sexual partners, persons who shared needles in the injection of intravenous drugs, and "patients with diseases such as Hemophilia A who require frequent transfusions involving large quantities of blood and blood products." No mention was made of the risk of transmission through blood transfusions. This brochure was intended for the general public and was distributed to hospitals, public health clinics, and physicians. In contrast, in an AIDS document for health care workers that was prepared by the ministry in the same year, recipients of blood transfusions were described as at risk of contracting AIDS.

The Ontario Public Education Panel on AIDS, established by the Ministry of Health in 1985, began distributing fact sheets about AIDS in February 1986. One of these, "Detecting AIDS," said that the virus that caused AIDS was transmitted through blood and blood products, but only persons who had received "many" transfusions between 1980 and late 1985 were advised to undergo testing for HIV antibody. In that fact sheet, and in a brochure issued by public health authorities in Newfoundland in 1985, there was no mention of the "window period" of early infection during which the antibody could not be detected. The Newfoundland pamphlet did not ask groups at high risk to refrain from donating blood and did not advise persons who had received blood transfusions before the autumn of 1985 to consider being tested.

Public health authorities in Alberta recognized the importance of public education, as explained in the issue of the provincial *Epidemiologic Notes and Reports* of 23 December 1986:

Even though tests to detect antibody to the AIDS virus are now available to assist in the elimination of potentially infectious units of blood and plasma, it is important to recognize that information and education remain crucial elements in any AIDS prevention program and that they continue to be relevant to the safety of blood and blood products. In that respect, measures to limit the transmissions of [HIV] by whatever means will be most effective in communities which are as well informed as possible about the disease, how it is transmitted and how donors can assist in assuring a safe blood supply by being alert to donor suitability criteria.

By this time, Alberta had the fourth highest rate of AIDS in Canada. It did not, however, begin a public education campaign about AIDS until the summer of 1987.

In some provinces, public health authorities responded to questions from the media but did not actively distribute information about AIDS. Even intensive campaigns were sometimes short-lived. In late 1985, the Department of Health of Manitoba began a campaign that included radio and newspaper advertisements, a telephone information line, and a brochure distributed to health units, pharmacies, and community groups. In the subsequent years,

despite recommendations from the provincial advisory committee on AIDS, the campaign languished. The government did not resume its efforts until late in the 1980s.

When they were asked during their testimony why they had not begun educational campaigns earlier, some public health officials said they had believed that the Red Cross and community organizations were taking the necessary measures to inform the general public about AIDS. The answers of the chief epidemiologist of Saskatchewan revealed a state of knowledge that was common in many parts of Canada. In 1983, he said, he estimated that the risk to the residents of his province was low; lack of information about AIDS made effective preventive action difficult; he did not know that some Saskatchewan residents were already infected; he was not accustomed to infectious illnesses with such a long incubation period; he did not know the number of hemophiliacs who resided in Saskatchewan or the size of the homosexual population; and he believed that the benefit from an expenditure of \$10,000 on educational pamphlets would be low and that the money could be better spent in other ways.

Alerting hemophiliacs to the risks of AIDS

During 1982 and 1983, a link was established between the use of blood products and infection with AIDS. Both hemophiliacs and their sexual partners were at risk of infection.

In Ontario, employees of the City of Toronto public health department kept abreast of the medical literature about the transmissibility of AIDS through blood during the early 1980s. Dr Alexander Macpherson, Dr Richard Fralich, and William Mindell understood that cryoprecipitate was safer than factor concentrates, believed that U.S. blood products manufactured from paid plasma donors were more dangerous than blood products derived from Canadian volunteer donors, and were aware of the recommendations of the medical and scientific advisory committee of the Canadian Hemophilia Society. Dr Macpherson and his staff discussed these issues with the local board of health, with physicians who treated hemophiliacs, and with representatives of the Canadian Hemophilia Society. In April 1983, Dr Macpherson wrote to a journalist to correct statements published in an article about AIDS. He explained that cryoprecipitate, which was derived from individual donations of blood, was safer than factor concentrates, which were made from the pooled plasma of thousands of donors, and that concentrates made from paid donors in the United States were considered less safe than those made from plasma donated by Canadian volunteers. He referred the journalist to recommendations made by the medical and scientific advisory committee of the Canadian Hemophilia Society and published in the *Canada Diseases Weekly Report* in the previous month. In July 1983, Mr Mindell, the coordinator of community health information in Dr Macpherson's department, sent

AIDS Questions from Hemophiliacs and Their Families to public health nurses in the sexually transmitted disease clinics operated by the City of Toronto. In that document, he listed the number of hemophiliacs who resided in the province, described the two comprehensive-care clinics for hemophiliacs in Toronto, and urged public health nurses to encourage hemophiliacs to associate themselves with the clinics to obtain current information about AIDS and to be monitored for indications of AIDS. He also recommended that hemophiliacs and their families register with the Ontario chapter of the Canadian Hemophilia Society to keep informed about preventive measures against the transmission of AIDS. He attached to his document the Canadian Hemophilia Society's "Update of AIDS for the Canadian Hemophiliac and the Medical Profession," in which it was recommended that hemophiliacs who had never previously used concentrates be treated only with cryoprecipitate and that hemophiliacs postpone elective surgery.

Public health officials in most provinces did not take measures before the autumn of 1985 to inform hemophiliacs and their sexual partners about preventive actions they could take. In general, provincial public health officials believed that the physicians who were treating hemophiliacs were best placed and suited to counsel their patients about AIDS and the risks to their sexual partners, and they believed that the physicians were performing this role.

The treating physicians did not always welcome the intervention of public health officials. Dr Margaret Fast, director of communicable disease control in Manitoba, said that members of the Canadian Hemophilia Society were "suspicious of public health" and that "we had a great deal of difficulty determining exactly what was being done within and for the hemophilia population medically. Physicians were very reluctant to share information about the status of their patients." On behalf of the directors of the Ontario Hemophilia Comprehensive Care Centres and the Ontario chapter of the Canadian Hemophilia Society, Dr Irwin Walker wrote in 1986 to the provincial director of public health. He asked that public health officials refrain from communicating with HIV-positive hemophiliacs and their sexual partners to give them information or counselling about AIDS. He said that "any public health contact of a seropositive hemophiliac or his sexual partner without prior consultation with the regional HCCC [Hemophilia Comprehensive Care Centre] Director would be redundant, unnecessary, and quite possibly harmful to the best interests of our patients, their families, and other relationships."

Alerting the gay community

From the outset, AIDS was associated with homosexual men, who were quickly recognized as the largest group of persons at risk of contracting the new disease. After it became evident that the disease was transmissible through blood, the Red Cross issued press releases, in March and July 1983, asking sexually active homosexual and bisexual men with multiple partners

not to donate blood. In some provinces, public health authorities reinforced this message, along with advice about safe sexual practices. In others, little was done to make contact with the gay community.

Public health officials in Manitoba had established connections with the province's gay communities during the late 1970s by counselling their members about preventive measures against syphilis. Those contacts proved valuable when efforts had to be made in the early 1980s to contain AIDS. From 1982, public health workers at the province's sexually transmitted disease clinics routinely advised gay and bisexual men not to donate blood to the Red Cross. The Cadham Provincial Laboratory-Preventive Medical Services committee recognized the importance of giving information about AIDS to gay and bisexual men and of maintaining contact with the leaders of the gay community, and when a provincial advisory committee was established in 1985, it included representatives from the gay community. Dr Hammond, the chair of the advisory committee, explained in testimony that

this was not a disease of uniform risk to everyone in society. There were what were called high risk groups. Over 80 per cent of AIDS patients were individuals who were gay ... Obviously, if we were going to have control strategies, we had to be able to be effective and work with those communities ...

We had a number of meetings with them early on and recognized that we were not very experienced in dealing with issues in those risk groups, particularly the gay and bisexual male areas.

We needed their expertise and their input, so that is why they were made partners in this process.

In Toronto, the public health department was also quick to respond to the emergence of AIDS. The city had one of the nation's largest populations of homosexual men, many of whom visited New York and other cities in the United States. In the summer of 1983, the department distributed a pamphlet about AIDS to gay bars and bath houses. It said that AIDS was believed to be "caused by an infectious agent such as a virus which can be spread through intimate sexual contact or through exposure to infected blood." Sexually active gay men with multiple partners were asked not to donate blood to the Red Cross and were encouraged to obtain further information from the department's telephone information service, the Hassle Free Clinic, the AIDS Committee of Toronto, the Ontario Advisory Committee on AIDS, or sexually transmitted disease clinics at hospitals in Toronto.

The public health authorities of Manitoba and Ontario gave financial support to the educational activities of gay organizations in the early years of AIDS. The Department of Health of Manitoba contributed money for a forum about AIDS organized by the Manitoba Gay Coalition, and also gave grants to the Winnipeg Gay Community Health Centre, which provided medical

care, education, and counselling. The City of Toronto financially supported the educational work of the Hassle Free Clinic in gay bath houses, as well as the AIDS Committee of Toronto. A Toronto staff member sat on the committee's board of directors. The Ontario government was also a regular financial supporter of the committee.

Both the provincial authorities in Manitoba and the local public health authorities in Toronto resisted organized attempts to have gay bath houses closed. They argued successfully that the bath houses afforded a means of access to gay and bisexual men who sought anonymous sex and could not be reached in other ways. Public health employees in Manitoba made regular visits to the bath houses to distribute literature about AIDS, provide counselling, and distribute condoms. In Saskatoon, staff members of the local health unit visited gay bars to distribute material about AIDS, co-sponsored a seminar on AIDS with gay and lesbian organizations, and, after 1985, hung posters in gay bars announcing the availability of provincial testing for HIV antibody.

Representatives of the gay community took part in the work of the Ontario Public Education Panel on AIDS, one as a member of the panel, another as a resource person. In its three-year existence, six fact sheets were prepared by the panel and distributed to the public. In two of the sheets distributed in February 1986, gay and bisexual men were asked not to give blood in order to learn their HIV status, but to arrange with their physicians for a test through the provincial laboratory.

Some, but not all, senior health officials in the Saskatchewan and Alberta ministries of health were reluctant to establish communication with the gay community in an effort to control the spread of AIDS. In Alberta, Dr John Waters, the director of communicable disease control and epidemiology, and Dr Barbara Romanowski, the director of the sexually transmitted disease service, believed that giving information to and counselling gay and bisexual men were important public health measures. They decided not to comply with the requests of their superiors to remove sexually transmitted disease clinic workers from the gay bath houses. Dr Romanowski and members of her staff visited gay bars and gay bath houses to impart information about AIDS to this high-risk group. Gay and bisexual men were told to use condoms, to limit the number of sexual partners, and to remove themselves from the blood donor pool permanently. Dr Romanowski gave the Red Cross the names of persons who she believed should be prevented from giving blood because of their high-risk behaviour.

In other parts of Canada, little effort was made during the early 1980s to encourage homosexual men to take precautions against contracting AIDS and to refrain from donating blood. Despite this indifference, physicians, gay organizations, and local medical officers of health urged their provincial departments or ministries of health to contact the gay community to impart this information. In the letter of 29 May 1984 quoted above, Dr Willoughby

urged the Minister of Health of British Columbia to distribute educational material about AIDS to the gay community because "for probably the rest of this decade, the most effective treatment will be prevention." In New Brunswick, Professor Getty told the provincial director of public health services in September 1985 that a public information campaign aimed at homosexual men could be carried out through pamphlets in doctors' offices, pharmacies, gay clubs, and other public places, articles in local newspapers, discussion groups, posters in strategic areas, and a telephone service through which persons could receive information anonymously.

Some officials believed that gay organizations could be more effective than the public health service in reaching the gay community. For example, one official in Nova Scotia said that "[w]e felt we did not have a strong chance of success of directly intervening in educating high-risk persons, and we felt the community-based groups would do a much better job, where they have a privileged ear and a privileged voice." Gay organizations had, in fact, responded quickly to the emergence of AIDS with pamphlets, meetings, and telephone "hotlines." In most provinces, however, senior provincial health officials were reluctant to give financial assistance to the educational work of such organizations, in part because of the sexual orientation of their members.

For example, in February 1984 the Minister of Health of Saskatchewan received a letter from the board of directors of the Gay Community of Regina inviting him to attend a conference in March at which physicians, psychiatrists, and other health care workers would present information about AIDS. The board asked the Minister to welcome participants and to explain the government's position on controlling AIDS. On a copy of the letter in the departmental files, the words "go to hell" appear in handwriting. At the hearings, the provincial epidemiologist of Saskatchewan said that "there was a lack of understanding and support for the gay community within the government at that time" and that "I believe that the attitude of the government of the day, besides being large 'C' conservative, was small 'c' conservative, and they had some concern with regards to this constituency that they believed they represented from being seen to be too actively in support of the gay community."

The Ministry of Health of British Columbia refused financial support to community organizations for educational programs about AIDS from 1983 to 1986. On one occasion, in February 1985, the ministry explained in its internal publication, *Infoback*, that a request from AIDS Vancouver for a financial contribution towards two brochures about AIDS addressed to gay men had been rejected because it "might imply total endorsement of the contents which included various sexually explicit slang terms and a general advocacy of homosexuality." By this time, public health workers in other jurisdictions had discovered that explicit language was necessary to convey information about safe sex effectively.

In their testimony, some public health officials said they had not made contact with the gay communities in their provinces because they had not known how to reach them. Gay organizations existed throughout the country in the early 1980s, however, and many were listed in the local telephone books.

In British Columbia, Alberta, and Saskatchewan, provincial grants to community groups for education about AIDS were not made until the late 1980s. The Gay Association in Newfoundland did not receive financial support from the government in the early years of the disease. When the chief medical officer of health of Prince Edward Island testified in August 1994, AIDS P.E.I. had not received provincial financial support, despite his efforts.

Contact Tracing

Contact tracing is a method used by public health officials to control the spread of infectious or communicable diseases. Infectious diseases can be spread either through common sources, such as water or food, or, like communicable diseases, directly from person to person. The purpose of contact tracing is to seek out the persons who have been in close contact with an infected person. The contacts are then counselled about the ways in which the disease is transmitted and about measures they can take to prevent or reduce its spread to themselves and to others. They may be referred to their family physicians or to public health clinics to find out whether they have been infected. If they are infected, they can be offered medical treatment and further counselling.

By the 1970s, because of successful control measures, including the development of vaccines for polio, smallpox, tuberculosis, and measles, most contact-tracing programs were directed at sexually transmitted diseases, such as syphilis and gonorrhea. Public health authorities operated special clinics at which they offered counselling and treatment to persons infected with sexually transmitted diseases and to their sexual partners. Testing for infection with these diseases was usually performed at public health laboratories.

From 1981 to 1983, the *Canada Diseases Weekly Report*, published by the Laboratory Centre for Disease Control, and the *Morbidity and Mortality Weekly Report*, published by the U.S. Centers for Disease Control, reported that homosexual men were at high risk of contracting AIDS through sexual contact. There was increasing evidence that the causative agent of AIDS was blood borne and could be transmitted by blood products, by blood transfusions, and by shared hypodermic needles used by drug addicts. In 1983, the development of AIDS in three Canadian hemophiliacs was evidence of a link already revealed in the United States between AIDS and the blood products on which hemophiliacs depended. In the spring of 1985, the first official report was made of a transfusion-transmitted AIDS case in Canada. In light of the transfusion-related infections reported in the United States, a Canadian case was not unexpected. At that time, there were 196 cases of AIDS in Canada.

Until the infectious agent that caused AIDS was discovered in 1984 and a test was developed to detect its presence, public health officials had few ways to stop its spread. One of the methods available was a program of contact tracing and counselling. The preventive measures recommended in the counselling changed as the knowledge of AIDS and its modes of transmission increased. Available measures included advising persons with AIDS and their contacts to use condoms, to avoid sharing needles, and to refrain from donating blood. It also involved asking infected persons and their contacts whether they had donated blood; if they had, the recipients of the contaminated units could be traced with the cooperation of the Canadian Red Cross Society (Red Cross) and the hospitals where the transfusions took place. The recipients then would be given the same advice as the sexual contacts of persons infected with AIDS.

Tracing the contacts of AIDS-infected persons before the introduction of testing

Despite the increasing number of cases of AIDS reported in Canada in 1983, 1984, and early 1985, no provincial department or ministry of health took measures to establish a program of contact tracing for the disease until the summer of 1985. Most provinces did not implement a contact-tracing program for AIDS until 1987 or 1988.

Most provincial public health legislation did not require medical officers of health expressly to trace and counsel the contacts of persons infected with a communicable disease. Most provincial legislation did, however, provide that medical officers of health take the measures that they believed would be most effective to prevent and to contain communicable diseases. In Ontario, for example, the *Public Health Act* included the following provision:

where a communicable disease is found or suspected to exist in a municipality, the medical officer of health and local board shall use all possible care to prevent the spread of infection or contagion by such means as in their judgment is most effective for the public safety.

In New Brunswick, regulations under the *Public Health Act* authorized the district medical officer of health to

exercise all measures which have proven practical in Public Health Administration and which have been accepted by Public Health authorities, to carry out any preventive measure he considers necessary to control and prevent the diffusion of any notifiable disease.

Contact tracing by public health officials was hampered by the fact that, during the early 1980s, AIDS was not a notifiable disease in all provinces. That is, family physicians and other health care providers were not required

by law to report to public health authorities the names of patients with it. Although some persons with AIDS may have been known to public health officials because they had gone to sexually transmitted disease clinics to be diagnosed and counselled, many persons with AIDS were not known to public health officials because they were cared for by family physicians, infectious disease specialists, or hospital physicians. Without a requirement to report AIDS cases to public health authorities, public health officials could not carry out comprehensive contact-tracing programs for persons with AIDS.

AIDS was treated as notifiable in British Columbia beginning in 1983 under a provincial regulation requiring physicians to report a communicable disease "which becomes epidemic or shows unusual features." AIDS was made notifiable or reportable by legislative amendment in Ontario and Alberta in 1983, in New Brunswick and Saskatchewan in 1984, in Nova Scotia and Prince Edward Island in 1985, in Quebec in 1986, and in Manitoba and Newfoundland in 1987.

In testimony during the hearings in most provinces, provincial public health officials gave several reasons why contact tracing for AIDS had not been conducted with the same rigour as for other communicable diseases. Several said that contact tracing was inappropriate for a disease like AIDS for which there was no known cure or treatment. They said that there was little purpose in contact tracing before testing for the presence of HIV antibody became available in the autumn of 1985, because the partners of infected persons could not know with any certainty whether they had contracted the virus and might be caused anxiety without any hope of remedy. The director of communicable disease control and epidemiology in Alberta testified that the lack of medical treatment was an important factor in the decision by public health officials in Alberta not to institute an active program of contact tracing for AIDS:

Public health's role is the control of communicable diseases in the community. There is a lot of argument about whether contact tracing really plays a significant role in that control. For diseases like syphilis, where there is a specific intervention that can be offered, where treatment can be offered and where an individual who has been infected can be cured, there is felt to be a greater obligation to provide follow-up ... For many of the other diseases, particularly where there is nothing we can specifically offer, it is not as frequently done.

Other public health officials testified that a contact-tracing program for AIDS would have required significant financial resources, which might be used more effectively for other activities. They said that among homosexual men – members of the group at highest risk of contracting AIDS – there were some who had anonymous sexual relations with many partners. They did not believe that the funds that would be required to train and pay employees to

trace contacts, especially in such cases, would be a worthwhile expenditure of public funds.

The National Advisory Committee on AIDS, an expert committee advising the Minister of National Health and Welfare, also discouraged provincial public health officials and physicians from tracing contacts. In a document published on 26 April 1984, it said:

Contact tracing is not necessary nor is it appropriate, and, in fact, is discouraged. In the instance where a sexual contact presents himself/herself to a MOH [medical officer of health]/physician, assurances are all that can be offered.

It also said:

There is no specific basis to defend any more stringent measures aimed at prevention: i) There is no legal responsibility to institute contact tracing. ii) Until results from ongoing epidemiologic studies are forthcoming, no knowledge exists relating to the risk of sexual contacts. iii) Nothing can be offered the contact to date since there is no diagnostic test specific to tell whether a contact indeed has been exposed to the purported "AIDS agent." Of course, if signs or symptoms arise in the contact, appropriate work-up should be instituted.

Public health officials in British Columbia followed the committee's recommendation about contact tracing despite the fact that they normally traced the contacts of persons infected with sexually transmitted diseases. The reasons, according to the director of the epidemiology division of the provincial Ministry of Health, were that the risk of infection appeared low in British Columbia, no test for the virus was available at the time, and "the National Advisory Committee on AIDS was the expert group in this matter."

The testimony of public health officials in Nova Scotia, Alberta, and Saskatchewan characterizes the positions on contact tracing taken by some provincial public health departments before testing for AIDS was available. Both Dr Wayne Sullivan, the administrator of community health services in Nova Scotia, and Dr Pierre M. Lavigne, that province's epidemiologist, said a patient's physician had the primary obligation to trace the contacts. The doctor-patient relationship, particularly a long-standing relationship, was conducive to disclosure by the patient of the identity of persons with whom he or she had sexual relations, shared needles, or engaged in other conduct that placed these persons at high risk of infection with AIDS. These public health officials expressed the opinion that a physician had both a legal and ethical obligation to trace the contacts of his or her patient who showed indications of AIDS. Dr Sullivan said the ultimate responsibility for ensuring physicians met that obligation rested with the College of Physicians and

Surgeons. Dr Lavigne said the provincial public health service had an obligation to ensure that contact tracing was carried out by the patient's physician. Both agreed it was incumbent on the physician to ask for help from public health officials if he or she found it difficult to trace or counsel the partner or partners of persons with AIDS.

In Alberta, there was uncertainty as to who was responsible for tracing contacts of individuals with AIDS. Dr John Waters, the provincial director of communicable disease control and epidemiology, said attending physicians were expected to notify and counsel partners of their HIV- and AIDS-infected patients, but public health authorities might provide support in "particularly sensitive cases or in cases where either the physician or person involved was not comfortable doing [it] themselves." In a briefing note in September 1985, he said that "patient management is individualized, with the attending physician and existing hospital services assuming the major responsibility for care, counselling, and contact identification." He also said that local public health authorities should "assist as requested and ensure that there is appropriate follow up and surveillance."

Saskatchewan is another province in which AIDS was dealt with in a manner different from other notifiable sexually transmitted diseases. Health units performed contact tracing for syphilis and hepatitis, both of which were designated as notifiable diseases in the regulations under the *Public Health Act*. There was, however, no attempt by public health officials to find the contacts of persons with AIDS. Reliance was placed upon the physician of the infected person to perform this task. Some health units, such as the Saskatoon Community Health Unit, did provide assistance to physicians who requested it.

Although they relied on physicians to trace and counsel the contacts of infected persons, many public health officials questioned whether this was an effective approach. For example, both Patricia Matusko, the director of sexually transmitted diseases in Manitoba, and Dr Waters agreed that leaving it to community physicians to notify contacts of persons with communicable diseases was not always appropriate, because some persons do not have family physicians, and "the relationship between the physician ... and the patient diagnosed with an STD [sexually transmitted disease] in the larger cities may be rather transitory." Dr Waters said that public health employees in Alberta's sexually transmitted disease clinics often had better training and more experience than the average physician in such tracing and counselling.

Measures were not taken to monitor whether physicians were tracing the contacts of their AIDS patients. Some provincial public health officials took the position that physicians would seek provincial assistance if they were unable to notify the contacts of their patients. As a senior public health official said:

We trusted physicians to notify sexual partners and spouses ... there has never been direct contact from public health to the spouses and partners

to ensure that they are being informed. We relied on the physicians' report with these patients for this but made it clear that public health would assist if necessary.

Alberta was the first province to insert a specific reference to contact tracing for AIDS in its legislation and was the only province to do so before provincial testing for HIV antibody began in late 1985. In August 1985, Schedule 4 of the Communicable Diseases Regulations under the Alberta *Public Health Act* provided that medical officers of health "shall attempt to identify sexual contacts" of persons with AIDS.

Contact tracing after the introduction of HIV testing

The Red Cross began routine testing of all blood donations for the presence of HIV antibody in November 1985. At about the same time, the provinces made testing available through their own public health laboratories or that of another province. This permitted contact tracing to begin earlier, as soon as infection with HIV was detected, that is, in the asymptomatic stage when it was most likely that infection of another person or contamination of the blood supply could occur without anyone being aware of it.

Persons who were tested for the antibody to HIV at the provincial test sites were not usually required to disclose their names. In Nova Scotia, nominal testing was required, that is, the tested blood sample and resulting report identified the tested person by name. Most of the other provinces permitted coded, or occasionally anonymous, testing. With coding, only the physician requisitioning the test and his or her patient could know to whom the result referred. With anonymous testing, only the tested person knew to whom the result referred. Coded and anonymous testing made it more difficult, but not impossible, for public health officials to find the contacts of an infected person. In British Columbia, public health officials distributed a form to everyone who underwent HIV-antibody testing at the provincial test site and to the physician who requisitioned the test. The form asked persons who tested HIV positive to give a list of their sexual contacts to public health. They were told not to write their names on the form so that neither public health officials nor the contacts would know the identity of the person who had tested positive. The use of such a form would have allowed public health officials to communicate with the contacts of HIV-infected persons even in provinces in which testing was coded or anonymous.

In some provinces, HIV, as opposed to AIDS, was not reportable. As a result, public health officials did not have the information needed to contact persons infected with HIV. HIV became notifiable or reportable in Nova Scotia in October 1985, in New Brunswick in April 1986, in Newfoundland and Prince Edward Island in 1987, and in Saskatchewan and Manitoba in

1988. HIV was not made reportable in British Columbia, Alberta, or Quebec in the 1980s. In Ontario, HIV was not expressly designated as notifiable, but a section in the *Health Protection and Promotion Act*, which came into effect in 1984, required that physicians report "an agent of a communicable disease."

The provincial governments, for the most part, did not collaborate with the Red Cross in tracing persons who had received infected blood components or blood products. When the provincial governments instituted contact-tracing programs for HIV and AIDS, the programs were often confined to the sexual partners of infected persons, the traditional approach used in the provincial sexually transmitted disease clinics.

With very few exceptions, officials at the Red Cross blood transfusion service were not willing to disclose to public health authorities the names of donors who tested positive. A letter sent in October 1985 by Dr Martin Davey, the assistant national director of the Red Cross blood transfusion service, to Dr Max Gorelick, the medical director of the blood centre in Halifax, explained the Red Cross's position with respect to the disclosure of such names. In it, Dr Davey said that the Red Cross would not report HIV-antibody test results to provincial departments of health. "Reservations about the utility, confidentiality, and effects on donor recruitment of reporting have led the CRC [Canadian Red Cross] to believe that it should not be required in Canada." He added that, if provincial laws were to require that the names of HIV-positive blood donors be reported, only confirmed positive results would be disclosed to public health authorities.

The Red Cross's position prompted the Minister of Health in Nova Scotia to make a regulation in December 1985 that required the Nova Scotia division of the Red Cross blood transfusion service to disclose any information requested by the provincial epidemiologist. This included the names of donors, the results of enzyme-linked immunosorbent assay (ELISA) tests and other tests performed on donated blood, and when and where the donor gave blood. The regulation made under the Nova Scotia *Health Act* read, in part, as follows:

The Canadian Red Cross Society, Nova Scotia Division, its officers, servants and agents, shall immediately provide to the Provincial Epidemiologist, Dr Pierre M. Lavigne, or his successor, upon receipt from him of a written request, such information about the Society's blood supplies in Nova Scotia as he in his sole discretion deems appropriate. Without limiting the generality of the foregoing, the Provincial Epidemiologist may request the identity, address, and telephone number of a donor or donors, the name of the donor's physician (if known), the date and place of donation, the places to which donated blood was shipped, and the results of ELISA tests, or other screening tests, performed on donated blood.

Public health legislation in some provinces required directors of laboratories to report the results of positive tests for AIDS or its causative agent. Such legislation gave public health officials the authority to compel Red Cross laboratories that conducted HIV testing to disclose the names of donors who tested positive. For example, a provision of the Ontario *Health Protection and Promotion Act* provided that

[T]he operator of a laboratory shall report to the medical officer of health of the health unit in which the laboratory is located each case of a positive laboratory finding in respect of a reportable disease, as soon as possible after the making of the finding.

Some public health officials testified that they did not seek to trace persons who had received blood components from or blood products made with the plasma of HIV-infected individuals, because they were prevented from disclosing the names of those infected persons to the Red Cross. In British Columbia, Prince Edward Island, and Ontario, the legislation permitted medical officers of health to convey this information with the consent of the infected persons. Although this was permitted, it was not done routinely.

Another reason put forward by public health officials for not attempting to locate and counsel persons who had received HIV-infected blood components or blood products was that the Red Cross had established trace-back and look-back programs. Look-back refers to the process of finding recipients of blood components from an infected donor. Trace-back refers to the process of finding a donor after a recipient of a blood component contracts HIV or AIDS. The Red Cross did not have a national policy on look-backs until 1987.

In 1986, a meeting of the Canadian Urban Medical Officers of Health and representatives of the National Advisory Committee on AIDS was held to discuss public health issues related to AIDS. A majority of the participants agreed that "contact tracing for HTLV-III/LAV [HIV] infections was not justified at this time." At the beginning of 1987, when the anti-viral drug azidothymidine (AZT) became available in Canada, the National Advisory Committee on AIDS changed its position regarding contact tracing. The committee recommended that contact tracing be carried out for persons who might not have known they had been exposed to HIV. The recommendations were published in the issue of the *Canada Diseases Weekly Report* of 31 January 1987:

The following recommendations are based on the principle that individuals who may have no reason to suspect that they may have been exposed to HIV should have the opportunity to know that they may have been so exposed.

1. With the goal of preventing perinatal transmission of HIV, the highest priority for contact tracing must be women of child-bearing age. In many instances, these women may not be aware that they have been exposed to HIV and, therefore, may proceed to become pregnant with concomitant risk to others and themselves. Current recommendations are that infected women postpone pregnancy until more is known about the risk of overt illness during pregnancy and the risk of delivering an infected infant. In the instance where the index male is unwilling to inform his female contact(s) (sexual or needle-sharing), the physician should take appropriate steps to ensure that these women are informed that they have been exposed and should offer to provide or arrange for counselling and voluntary testing.
2. Infected patients should be encouraged to refer sex partners or persons with whom they have shared needles to their health-care provider for evaluation and/or testing. If patients prefer, the physician with patient's consent or where authorized by law, may request that trained health department professionals be made available to assist in notifying their partners and counselling them regarding evaluation and/or testing.
3. Intensive investigation of transfusion-related AIDS cases is essential to trace potentially asymptomatic unknowing blood donors who may otherwise donate blood or have unprotected sexual intercourse. Following identification of the infected donor(s), tracing of their contacts is required. Such contacts include sexual partners and recipients of blood/blood products who should be offered counselling and voluntary testing.

Seroreactive blood donors should be counselled by their physicians regarding the significance of their test results. They may wish to be retested. Their sexual contacts should be given high priority for counselling and voluntary testing because they may be among those least likely to realize that they have been exposed. The Canadian Red Cross should report to the local Medical Officer of Health the names of seroreactive donors that the Society has not been able to locate. The Medical Officer of Health should take the responsibility for locating these donors and for identifying and counselling those individuals who refuse to see a physician for follow-up.

The establishment of contact-tracing programs in the provinces

In British Columbia, public health officials began to consider the issue of contact tracing when HIV-antibody testing was imminent. Within a few weeks of the Federal-Provincial Conference on AIDS on 4 July 1985 at which the Red Cross discussed its plans to implement testing, Dr Timothy Johnstone, the director of the epidemiology division in the British Columbia Ministry

of Health, suggested to Ron de Burger, an assistant deputy minister, that physicians in the community be given the responsibility for tracing the contacts of their HIV- and AIDS-infected patients:

[A]t the provincial level, the physician/patient and public health/patient interface now becomes the real issue. Assuming diagnostic testing is done through individual physicians at V.D. [venereal disease] Control Laboratory, we have to decide how (and by whom) to ascertain contacts of infected individuals, and how to notify contacts, without breaching the confidentiality of the "case." And at every stage counselling on the implications of results will be needed. Possibly it could all be done through physicians; i.e. results could be made available to doctors only, lists of contacts obtained through counselling could be contacted, asked to choose a physician (who would be sent the appropriate information) and asked to contact him/her for counselling and possible testing, etc. ...

As opposed to present V.D. Control where it is a public health responsibility to ensure cases are treated to prevent spread, with HTLV-III [HIV], the only "treatment" available is counselling and hopefully life style modifications to prevent spread. Thus confidentiality and credibility of the public health response are of primary importance.

In December 1985, Dr Michael Rekart, the director of sexually transmitted disease control in the province, recommended to Mr de Burger that "active" contact tracing for HIV and AIDS patients be conducted in British Columbia. Dr Rekart took the position that contact tracing for HIV and AIDS ought to be similar to the partner notification program for syphilis and gonorrhea in order to protect the public and stop the spread of AIDS. He grouped patients into three categories:

1. Group A – patient well informed, patient will do the notification;
2. Group B – the patient would like someone to notify them [the contacts], but is unwilling to do it himself;
3. Group C – the patient does not know their identity or simply is unwilling to notify himself or tell anyone.

Dr Rekart suggested that the government focus contact tracing on persons in group B. A form was to be given to all persons who tested positive and their physicians. A person who tested HIV positive was asked to list his or her sexual contacts. The form contained the following information:

Your blood shows antibodies to the AIDS virus. This means that you have been infected with this virus in the past and probably still carry it in your body and bodily fluids. You must assume that you can pass this virus on to others through sexual and blood contact. Your doctor has already discussed with you what this means.

PLEASE REMEMBER:

1. Do not donate blood, sperm, breast milk, organs, or other tissue.
2. Do not share needles.
3. Do not attempt to have children until you have discussed this with your obstetrician.
4. Tell your health care providers of your antibody test result so that they can take precautions; that means doctors, dentists, nurses, etc.
5. Tell your sexual contacts of your antibody test result so that they may seek medical advice.
6. Do not infect others, practice SAFE SEX only:
 - no anal intercourse
 - no oral genital contact
 - no exposure to your partner's urine
 - no new partners
 - no oral-anal contact

In order to stop this epidemic, it is important that your sexual contacts know that they have been exposed to this virus. Please list below those sexual contacts (since 1978) that we can notify for you and send this list to us in the attached envelope. Do not put your name on this form; we do not need to tell these contacts who you are.

Dr Rekart suggested to Mr de Burger that the employees of the provincial AIDS Testing, Evaluation, Counselling Clinic notify the contacts listed on the form by telephone. The contacts would be told that they may have been exposed to the virus, and that they should consult a physician or visit the clinic. The identity of the HIV-infected person would not be disclosed to the contacts.

At the end of April 1986, Dr Rekart received approval from Mr de Burger to proceed with the contact-tracing program. Four to 5 per cent of the persons who tested positive at the provincial laboratory returned the contact-tracing form to the Ministry of Health. Some of the forms were returned with the name of only one contact. Others listed as many as thirty sexual partners. Public health officials tried to reach these partners, and a record was kept of the number of persons notified. The record of the names of the partners was destroyed after they had been contacted.

In Ontario, the provincial AIDS advisory committee did not recommend contact tracing when it considered the issue in December 1985 because "containment and prevention of AIDS could best be achieved by education, emphasizing safe sexual practices" and "contact tracing is not cost effective at the present time." The position of the committee changed in October 1986. In a document entitled *Contact Tracing of Individuals with HTLV-III Infection*, the committee recommended that contact tracing be conducted for four groups of persons: homosexual and bisexual men who had been sexually active since 1977; intravenous drug users and others who share needles; heterosexual men and women who had been sexually active since 1978; and recipients of blood, blood products, and tissue from individuals who were found to be HIV positive. In contrast with most of the other provinces, Ontario had

a policy that sought to trace not only the sexual contacts of HIV-infected persons but also needle-sharing partners and persons who had received blood components from or blood products made with the plasma of HIV-infected persons.

The Ontario Ministry of Health endorsed the recommendations of the AIDS advisory committee and Dr Barbara Blake, the director of the public health branch, sent the document on contact tracing to medical officers of health in the province. She asked them to assess the effectiveness of the contact-tracing program proposed by the AIDS advisory committee. Dr Blake stated that the following issues should be considered: "the degree of cooperation of local physicians, the percentage of seropositive individuals contacted and the number of their contacts traced and counselled, and lastly the financial implications this has had for your health unit."

Dr Blake received a letter from Dr Irwin Walker, the chair of the medical and scientific advisory council of the Ontario chapter of the Canadian Hemophilia Society. Dr Walker asked public health officials not to trace the contacts of HIV-infected hemophiliacs:

We are now concerned about the local public health unit follow-up and contact tracing programs that are being developed for HIV seropositive individuals, including hemophiliacs and their sexual partners. In virtually every case these seropositive hemophiliacs and their sexual partners will be seen at a HCCC [Hemophilia Comprehensive Care Centre], regardless of the source of an HIV lab requisition or other notification made to the local public health unit. In this respect, any public health contact of a seropositive hemophiliac or his sexual partner, without prior consultation with the regional HCCC Director, would be redundant, unnecessary and quite possibly harmful to the best interests of our patients, their families and other relationships. Therefore, on behalf of the Ontario Chapter CHS-MSAC [Canadian Hemophilia Society, Medical and Scientific Advisory Committee] and Ontario HCCC Directors, I am requesting that you officially notify all local Medical Officers of Health of the existence and role of the HCCC in AIDS / HIV follow-up, and advise them to contact a regional HCCC Director, prior to any other direct public health activities, upon receiving notification of an HIV seropositive case that may be at all related to a hemophiliac.

Dr Blake forwarded Dr Walker's letter to medical officers of health in Ontario.

The City of Toronto, which had a large concentration of gay men, adopted a policy different from that of the province. In October 1986, Dr Alexander Macpherson, Toronto's medical officer of health, described to the board of health the approach of city public health officials to contact tracing. An HIV-infected person's physician rather than a public health official was to determine whether contact tracing was appropriate and, if so, the physician was

to notify and counsel the contacts. The decision to contact trace was to be based "on the likelihood that further transmission could be prevented." The department of health was available as a "back-up to these activities." In "The Role of the Department of Public Health in Human Immunodeficiency Virus Antibody Testing and Follow-Up," written by Dr Macpherson and distributed to members of the Toronto board of health, he said:

Epidemiologic information (age, sex, risk group, nature of contact) on sexual and significant blood contacts should be elicited from all identified seropositive individuals by the attending physician, and the value of informing contacts should be considered. The most important factor in the decision to inform contacts should be the likelihood that further transmission can be prevented. This will depend on the likelihood that the contact has been infected and the likelihood that the contact will transmit the infection to others. For example, remote or infrequent contacts are less likely to have acquired the infection than recent or regular contacts. Contacts who are members of high-risk groups in high-prevalence areas may already have been advised to take precautions to prevent transmission, and therefore there may be little to gain in tracing and informing them. In general, however, seropositive individuals should be encouraged to inform their contacts and advise them to seek medical advice, including antibody testing. If contacts are seropositive, they can take precautions to prevent further transmission. Contacts who are women of childbearing age should routinely be informed and tested for antibody because of the risk of AIDS to their offspring if they are seropositive.

Most of the information in this document was published in December 1986 in *Healthscape*, a quarterly newsletter prepared by the Toronto public health department for primary care physicians in Toronto. Dr Macpherson stressed that it was particularly important for family physicians to notify sexual contacts, particularly heterosexual contacts, in addition to the recipients of blood or organs donated by persons with HIV-positive antibody status.

Nova Scotia was one of the few provinces that decided to work actively with the Red Cross in tracing contacts and recipients of blood from HIV-positive donors. After a regulation was made in December 1985 requiring the Red Cross in Nova Scotia to provide information requested by the provincial epidemiologist, Dr Lavigne established a procedure to facilitate contact tracing. In a memorandum to Dr Gorelick, the medical director of the Red Cross blood transfusion centre in Halifax in March 1986, Dr Lavigne wrote:

Recipients of Potentially Contaminated Blood/Blood Products

When an individual who has a positive HTLV-III [HIV] antibody test gives a history of donating blood within the past 3 years (prior to November 1, 1985), this should immediately prompt further investigation, by

the health unit director who is involved. The date(s) of the donations should be ascertained so that I can forward a request to the medical director of the Red Cross, to provide me with all the pertinent information concerning these donations (e.g. product, unit number, hospital and date issued), so that we can trace the recipients. This information will subsequently be used to contact the appropriate hospital (administrator) to request the necessary identifying information. Investigation and follow-up will be carried out by the appropriate local Health Unit Director.

As is customary, initial contact will be made with the recipient's family / attending physician. He / she will be advised to arrange for HTLV-III testing for the patient and an appropriate plan for follow-up will also be implemented by the health unit director.

Transfusion-related cases of HTLV-III infections

Where the most likely source for positive HTLV-III test result is probably due to receiving blood or a blood product on only several occasions (2 to 3) within the last 3 years, further investigation should also be conducted to ascertain the HTLV-III antibody status of the donors that were involved. The procedures for investigation will be almost analogous to those for the "recipients" described above except for the fact that donors will be contacted by the Red Cross, using methods similar to those used for donors found positive as a result of screening.

Dr Lavigne explained the importance of these investigations as a means of preventing secondary infection:

While there is no treatment for HTLV-III [HIV] infection, there may nevertheless be significant benefits for the entire community, if we actively intervene to ensure that appropriate measures are being taken for controlling the disease, and minimizing further inadvertent spread to "sexual and blood contacts."

Dr Lavigne also discussed the importance of contact tracing in *Medical Guidelines for HIV Screening*, published by the Nova Scotia Department of Health in November 1987. In it, he said that it was incumbent on physicians to conduct contact tracing and that the department of health would take steps to ensure that partner notification and counselling in fact occurred.

The recommendations of the National Advisory Committee on AIDS in early 1987 stimulated the development of a contact-tracing program in Newfoundland. In April 1987, Dr Faith Stratton, the province's epidemiologist and a member of the Newfoundland AIDS advisory committee, met with the local medical officers of health and explained to them that she obtained information about HIV-antibody positive cases in the province from three sources: the public health laboratories, the Red Cross, and Dr Kaiser Ali, the medical director of the comprehensive-care clinic. It was agreed that

Dr Stratton should report cases to the appropriate medical officer of health, who would then notify the patient's physician, complete an epidemiological form, and offer help in tracing contacts. The tracing would be conducted by either public health officials or by the physician, and the form was to specify who would do it. In many instances, it was done by public health officials. The program was to extend to all contacts of HIV-infected persons.

In New Brunswick, at a meeting of district medical health officers in November 1987, it was decided that, although physicians should have the task of notifying partners of their HIV-infected patients, public health employees should be prepared to assist physicians when requested. The decision was made, in part, because the local health units did not have the financial resources to trace contacts. It was recorded in the minutes that "in order for physicians to do a good job of counselling and contact tracing, they will need specific support from public health in terms of information and professional consultative services. The resources to fulfill these needs are inadequate also."

In Alberta, at a meeting of the Alberta Advisory Committee on AIDS in July 1986, it was decided that priority in contact tracing should be given to the female sexual contacts of HIV-positive bisexual and drug-abusing males. Next in importance were the sexual contacts of HIV-positive persons identified through blood donations. The committee also decided that physicians should have the primary role in tracing contacts of their HIV-infected patients. Public health officials were available to help if requested.

At meetings of the Alberta advisory committee in 1988, some medical officers of health expressed dissatisfaction with their marginal role in contact tracing. Dr Bryce Larke, then the director of the Alberta AIDS Program, reported that some medical officers of health "have expressed concern that health units are not involved in contact tracing and questioned the future role of health units in the control of the disease." Dr Karen Grimsrud, deputy medical officer of the Edmonton board of health, said that "[h]ealth units have been cut out of the control of AIDS in this province," but "it is unrealistic to think they could contribute, given their current lack of funding in this area."

Like their counterparts in most other provinces, Alberta public health officials did not take special measures to ensure that the spouses and other sexual partners of hemophiliacs were told of the risk of infection and offered appropriate counselling. The testimony of Alberta's director of communicable disease control and epidemiology reflects the view of public health officials in other provinces: "It was the responsibility of the attending physician and not public health to have informed the wives of hemophiliacs that they were at risk of secondary infection. Public health did not follow-up to ensure that spouses were notified."

Saskatchewan and Manitoba did not develop a contact-tracing policy for HIV-infected persons until 1988. In January 1988, Dr Roy West, the chief epidemiologist in Saskatchewan, prepared a document in which he discussed

the propriety of treating HIV differently from other notifiable communicable diseases; he observed that such an approach "could have long-term implications for the total process of control of communicable diseases." Dr West wrote:

All persons who are seropositive and as many of their contacts as possible must be counselled regarding the risks from an [sic] transmission of HIV infection. Names of all seropositive individuals MUST be reported to the Medical Health Officer [MHO] by the physician. The MHO (and if necessary their staff) will ensure counselling and follow-up. This may be done by the physician or even the individual. The MHO must have the right and the information to ensure this is done.

On 12 January 1988, the Saskatchewan Advisory Committee on AIDS produced a contact-tracing protocol for medical officers of health. The physician and the medical officer of health were to decide on a case-by-case basis who would notify and counsel the contacts of the infected person. If the physician agreed to perform the contact tracing, no further action was required by public health officials. In cases in which the physician asked the medical officer of health to conduct the contact tracing, the obligation of the public health official to notify partners of the HIV-positive person was highly circumscribed:

If physician assumes responsibility for follow-up, MHO [medical health officer] will note physicians commitment and no further action is required. If physician requests MHO assistance our activity will be determined on a case by case basis, but generally restricted to:

- counselling individual about nature of disease, safe practices, and responsibility to advise relevant others
- counselling of contacts of prior six months, if demonstrated need is indicated.

In Manitoba, the importance of contact tracing for AIDS was recognized at the beginning of 1985. The Cadham Provincial Laboratory-Preventive Medical Services committee recommended that a registry of AIDS cases be created, one of the purposes of which was to facilitate contact tracing. The public health officials on the HIV subcommittee of the Manitoba advisory committee also recommended a formal contact-tracing program and a registry. Other members of the subcommittee took the position that the government should not be involved in partner notification and that no records or a registry should be maintained. As a result of this disagreement, no contact-tracing program for HIV and AIDS was established in the province until June 1988.

Commentary

Despite the value of contact tracing as a means of controlling the spread of infectious diseases, it was not used in most provinces to control the spread of AIDS before 1986. In some provinces, it was not used until 1988. Even then, its primary focus was the tracing and counselling of sexual contacts. Although sexual transmission was a proper concern, other modes of transmission should not have been ignored.

Before testing for the HIV antibody was available, the role of public health officials in contact tracing was limited, especially in provinces in which AIDS was not reportable. Public health officials knew about the persons with signs or symptoms of AIDS who went to provincial clinics for sexually transmitted diseases. Many other persons with AIDS were known to their family physicians or to infectious disease specialists, but not necessarily to the provincial authorities. Public health officials could have reminded physicians of the importance of their notifying and counselling contacts about ways to prevent the further spread of the disease, including the barrier methods of birth control and refraining from donating blood. They could have encouraged physicians to ask whether their patients with AIDS or the patients' partners had donated blood and to urge those who had donated to tell the Red Cross about their infection. A more comprehensive contact-tracing program of this nature could have had an impact on the contamination of the blood supply and the transmission of AIDS.

In most provinces, notifying and counselling the partners of persons with AIDS was considered the responsibility of the attending physicians rather than the public health officials, despite the fact that many public health officials believed most physicians had neither the time nor the training to perform the task effectively. In many cases, public health officials did not encourage physicians to notify and counsel contacts of infected persons and did not monitor whether it was done, although many offered assistance to physicians who found the task too difficult or time-consuming.

The implementation of HIV-antibody testing gave public health officials an opportunity to re-evaluate their policies for contact tracing. By November 1985, contacts could be tested to determine whether they were infected with the disease. Testing allowed persons who were infectious but not symptomatic to be counselled at an earlier stage in the disease. It is at this earlier asymptomatic stage that the preventive measures are most important as a means of limiting the spread of the disease. In some provinces, infection with HIV was made a notifiable or reportable disease, with the result that public health officials were to be given information they needed to conduct contact tracing.

Although the "do not donate blood" message was not as critical after the advent of testing as it was before, it remained important because contacts could still be in the window period and not identified as HIV positive by either the

alternative test sites or the screening tests performed by the Red Cross. Identifying persons who had tested positive and had donated blood was important in identifying "blood contacts." Tracing of these contacts was particularly important because the Red Cross did not have a national policy on look-backs until 1987.

The Red Cross and public health authorities rarely cooperated in efforts to notify and counsel the recipients of contaminated blood or blood products and their sexual or other contacts. The Red Cross believed it had a duty to respect its donors' privacy and was unwilling, with few exceptions, to disclose to public health authorities the names of donors who tested positive. In Nova Scotia there was a specific regulation requiring the Red Cross to give public health authorities information they requested, including the results of ELISA screening tests. In the provinces where HIV was reportable, the Red Cross was required to report the results of positive confirmatory HIV-antibody tests.

Some provinces did not develop a contact-tracing program for HIV or AIDS until 1987 or 1988. Many of the programs that were developed concerned themselves only with sexual contacts and not with recipients of blood components and blood products. The decision not to trace these recipients had serious consequences. The health of the recipients was put in jeopardy, as was the health of their spouses or other sexual partners. Moreover, the blood system was endangered because these persons, unaware they were at risk of contracting AIDS, might have donated blood to the Red Cross.

The Risk to the Sexual Partners and Children of Hemophiliacs

Soon after physicians and scientists learned that a new, life-threatening syndrome had appeared in different parts of North America, they recognized that it had several modes of transmission. Of these, at least three had serious consequences for hemophiliacs, their families, and their sexual partners. The evidence suggested that AIDS could be transmitted sexually, maternally (within the uterus or at the time of birth), and through the use of blood products. The degree of risk was heightened by a lengthy incubation period during which an infected person showed no indications of AIDS. As a result, hemophiliacs – infected through the blood products on which they depended for health – could unknowingly infect their sexual partners, who could in turn infect a child before or during birth and could infect other persons by donating blood.

The risks described in this chapter were not confined to the spouses or sexual partners and the unborn children of hemophiliacs. The chapter focuses on the partners and children of hemophiliacs as a special case for two reasons. First, hemophiliacs are dependent on blood products for their health and require special medical attention; they are a relatively small group in the Canadian population, and most of them could be reached through the Canadian Hemophilia Society and the hemophilia treatment centres. It was possible therefore to undertake specially designed measures to warn them and their partners of the risks of infection, advise them to undergo HIV-antibody testing once it was available, and encourage them to take extra precautions in sexual intercourse. Second, some wives of hemophiliacs donated blood regularly out of gratitude for the blood products on which their husbands depended. It was particularly important that they, who not only were more exposed to infection but donated more often than the general public, should be urged not to donate blood lest they should unknowingly contribute to the contamination of the blood supply.

Recognition of the sexual and maternal transmission of AIDS

The evidence that the syndrome later called AIDS was sexually transmitted was first reported in mid-1981 and grew increasingly compelling thereafter. The *Morbidity and Mortality Weekly Report*, a publication of the U.S. Centers for Disease Control, said in its issue of 5 June 1981 that the homosexuality of five young men who had *Pneumocystis carinii* pneumonia, one of the indications of AIDS, suggested "an association between some aspect of a homosexual lifestyle or disease acquired through sexual conduct." The *New England Journal of Medicine* of 10 December 1981 reported that the fact that "this illness was first observed in homosexual men ... suggests that a sexually transmitted infectious agent ... has a critical role" in its development. The *Morbidity and Mortality Weekly Report* of 18 June 1982 reported a cluster of cases of Kaposi's sarcoma, another indication of AIDS, and *Pneumocystis carinii* pneumonia in homosexual men in California, several of whom had had sexual contact with one another, and said that if infectious agents were causing the illnesses, the sexual partners of those men might be at increased risk of developing the same diseases. The report said that the men had not developed symptoms for nine to twenty-two months after the infecting sexual contact, demonstrating that infected persons could remain apparently healthy for a long time. An article in the issue of *Nature* dated 9 September 1982 reported "the increasing incidence of the epidemic and its apparent transmission by sexual contact, drug apparatus and blood products."

Published reports of heterosexual and maternal transmission soon followed. In October 1982, the U.S. Centers for Disease Control reported that opportunistic infections had been observed in five New York women, whose circumstances raised the possibility that the syndrome could be acquired by intimate heterosexual contact. The researchers stated that "the extension of this outbreak to women has important implications concerning the cause, pathogenesis, and mode of transmission of this new syndrome, and should alert the medical community to consider the spread of this outbreak to new populations." The *Morbidity and Mortality Weekly Report* of 17 December 1982 reported unexplained immunodeficiency and opportunistic infections in infants born to women who were either Haitian or intravenous drug addicts. The issue dated three weeks later contained two reports of immunodeficiency in heterosexual women whose only risk factor was that they were the "steady sexual partners" of men with AIDS. Their cases were said to support "the infectious-agent hypothesis and the possibility that transmission of the putative 'AIDS agent' may occur among both heterosexual and male homosexual couples." The *Canada Diseases Weekly Report*, published by the Laboratory Centre for Disease Control, summarized the U.S. report of unexplained immunodeficiency and opportunistic infections in infants in its issue

of 22 January 1983. An accompanying editorial note concluded that "[t]ransmission of an 'AIDS agent' from mother to child, either in utero or shortly after birth, could account for the early onset of immunodeficiency in these infants."

The *Morbidity and Mortality Weekly Report* of 4 March 1983 published the recommendations of the U.S. Public Health Service for interim measures to prevent the transmission of AIDS, sexually and through blood. The list of persons at increased risk of contracting AIDS included sexually active homosexual or bisexual men with multiple partners and the sexual partners of persons at increased risk of contracting AIDS. The report of 4 March said that the "[a]vailable data suggest that the severe disorder of immune regulation underlying AIDS is caused by a transmissible agent" and that recent reports suggest "the possibility of heterosexual transmission" and "have raised concerns about *in utero* or perinatal transmission of AIDS."

In May 1983, the *New England Journal of Medicine* published the results of a study that investigated immunodeficiency in a group of women whose only common risk factor was prolonged monogamous contact with a partner who had AIDS. The study concluded that the female sexual partners of heterosexual men with AIDS were at risk of acquiring the syndrome. In July 1983, the *Canada Diseases Weekly Report* reported two cases of AIDS, one of which was considered to be sexually transmitted, in women in the Eastern Townships of Quebec. That report said that the medical literature showed that "sperm is the ideal vehicle for transmission of AIDS among sexual partners."

The results of studies assessing the risk to sexual partners of hemophiliacs began to appear in August 1983. The first, published in the *Annals of Internal Medicine*, examined the immune status of the wives of five immune-deficient hemophiliacs who used factor VIII concentrates. All the women were found to have immunologic abnormalities. The researchers acknowledged that the abnormalities could be related to factors other than sexual contact with the women's husbands, but said that they "appear[ed] to be early immunologic manifestations of the acquired immunodeficiency syndrome [AIDS], and are therefore of considerable concern." The researchers recommended the continued study of the sexual partners of hemophiliacs.

More compelling evidence was published in January 1984 in the *Annals of Internal Medicine*. It reported a case of AIDS in a seventy-one-year-old woman, the wife of a hemophiliac, whose only apparent risk factor was infrequent sexual contact with her husband before he had developed indications of AIDS. The report suggested that AIDS could be transmitted heterosexually by an asymptomatic person and that the female sexual partners of hemophiliacs treated with factor concentrate might be at risk. The researchers concluded that the case "supports the theory that the occurrence of the syndrome among hemophiliacs who are treated with factor VIII concentrate is due to an infectious agent that can be transmitted heterosexually as well as parenterally through blood products." In October 1984, *Science* reported that

the causative agent of AIDS, the human immunodeficiency virus, or HIV, had been isolated from the semen of two patients with AIDS. In January 1985, *The Lancet* reported the first case of AIDS in the child of a hemophiliac and a statement that "concentrate-treated hemophiliacs may transmit this agent to their spouses or children, resulting in pre-AIDS or AIDS."

The response to the risk in the United States

The report in January 1984 of the possible transmission of AIDS from a hemophiliac to his seventy-one-year-old spouse led the U.S. National Hemophilia Foundation to issue its first advisory notice for hemophiliacs about sexual practices. In the notice, dated 3 February 1984, the foundation described the risk of transmission as "infinitesimally small" and suggested that patients and their treating physicians "consider" the use of condoms. It also said that:

Because of widespread media publicity about this case, some concern has been raised about the possibility that sexual partners of hemophiliacs may be at risk of contracting AIDS. There is no easy answer to that question as there are still too many unknowns about the complex nature of AIDS and how it is spread. In the medical and scientific community there are different points of view on this topic, but all agree that *if* sexual partners of hemophiliacs are at increased risk for AIDS, *this risk is remote*.

... we offer the following recommendation concerning wives and sexual partners of hemophiliacs.

If there is *any* risk of heterosexual transmission of AIDS among otherwise healthy hemophiliacs, it is truly remote. Individual patients and their treaters need to consider whether or not they wish to employ prophylactic methods (e.g. condoms) in continuing their sexual relations as a strictly precautionary and temporary measure until more is learned about AIDS.

While the above applies to *healthy* hemophiliacs, and their sexual partners who do not have AIDS symptoms, it is important for all patients and their families to realize that this recommendation is provided for your consideration as a *strictly precautionary measure*. It is *not* intended to suggest that the risk of AIDS to hemophiliacs is any greater than that which has already been reported. Of course, those hemophiliacs *who have been diagnosed* with AIDS or who are *strongly suspected* of having AIDS are urged to discuss with their physician or member of the treatment center team matters concerning their sexual activity. [Emphasis in original.]

The National Hemophilia Foundation modified its position considerably in an "AIDS Update" in March 1985. The reference to a "remote" risk continued, but the message about how to practise safe sex was more explicit,

parallels were drawn to the spread of the disease in the homosexual population, and patients were urged to "strongly consider the regular use of condoms." It said:

Several studies suggest that members of families who are in close contact with persons with hemophilia do not have an increased risk of developing immune suppression or AIDS. There have been reports of immune suppression and AIDS in sexual partners of patients who have developed AIDS, one of whom was a hemophilia patient who developed AIDS. If there is a risk of heterosexual transmission of AIDS by otherwise healthy hemophiliacs, it appears to be remote ... Scientific data are available which establish the transmission of AIDS when semen comes in contact with the circulatory system ... Given this knowledge of mode of spread of the virus among homosexual men, it may also be advisable for heterosexual couples to avoid rectal intercourse. Persons with hemophilia should strongly consider the regular use of condoms until more is learned about AIDS. There is no scientific data implicating transmission of AIDS through oral-genital sex in the hemophiliac population; however, it is recommended that this practice be avoided until further information is available. Those who have been confirmed or strongly suspected of having AIDS are urged to consult with their treating physician on the question of sexual relations.

The risk to sexual partners of hemophiliacs was discussed at a conference about AIDS convened by the U.S. Centers for Disease Control in Atlanta in April 1985; it was also said there that children born to HIV-positive mothers might be at risk. The following month, the National Hemophilia Foundation issued a medical bulletin in which it described a study involving ten hemophiliacs and their spouses. The study concluded that the virus might be sexually transmitted from seemingly healthy persons to their spouses and that the transmission of the infection to the fetus was a distinct possibility. Because of its "sensitive nature," the bulletin was intended for health care providers only. The foundation recommended that hemophiliacs be told to use condoms and postpone pregnancy, and that their spouses be told not to donate blood.

The physicians were told that an accompanying advisory notice, to be sent to hemophiliacs and to local chapters of the foundation a week later, would "likely produce distress for many hemophiliacs and their sexual partners." That advisory reproduced much of the information in the medical bulletin, and gave more details of several recent studies. The cautions were repeated in another medical bulletin and advisory notice that were published by the foundation in mid-summer 1985. The advisory notice set out explicit guidelines for safe sex, including information about the comparative risks of vaginal, anal, and oral sex and the psychological consequences of changing one's sexual practices. In September 1985, the foundation distributed a new "AIDS Update" about "intimacy and sexual behavior." In December 1985, it

announced that persons with hemophilia “should now consider that [HIV] is sexually transmitted.” It said that the sexual partners of hemophiliacs were exposed to a very significant level of risk and that couples should take steps to minimize that risk. It urged patients to use condoms regularly. Because of the risk of maternal transmission, it recommended that the spouses of hemophiliacs be tested for HIV before the couple sought to become pregnant.

The World Hemophilia AIDS Center issued similar precautions in January 1985, recommending that “the use of a condom is a reasonable approach to prevention.” Three months later, it repeated that recommendation in another publication.

Educational material from the Canadian Hemophilia Society

The Canadian physicians and associations involved in the treatment of hemophiliacs were aware of the growing knowledge about the risk to the sexual partners and infants of infected hemophiliacs. The physicians subscribed or had routine access to such peer-reviewed medical journals as the *Annals of Internal Medicine*, *The Lancet*, and the *New England Journal of Medicine*. Some also subscribed to or were sent copies of relevant articles from the *Canada Diseases Weekly Report* and the *Morbidity and Mortality Weekly Report*. The Canadian Hemophilia Society, most of its local chapters, and many physicians received the publications of the U.S. National Hemophilia Foundation, in which cases and studies were reported. Some of the physicians attended professional meetings and conferences where scientific advances were discussed. Several of them, including the chair of the medical and scientific advisory committee of the Canadian Hemophilia Society, attended the conference about AIDS convened by the U.S. Centers for Disease Control in April 1985. The meetings of the medical and scientific advisory committees of the Canadian Hemophilia Society and its local chapters were forums for the exchange of information, and physicians in different provinces communicated with one another.

Although the majority of hemophiliacs did not read the scientific literature, most of them received the publications of the Canadian Hemophilia Society or those issued by their local chapter of the society. Some local chapters organized medical symposia about AIDS for their members. In addition, many hemophiliacs and their spouses had long-standing relationships with the staff members of the comprehensive-care clinic they attended and sought information during their visits.

The earliest published response by the Canadian Hemophilia Society to news of the risk of AIDS was intended to allay concern. The bulletin published by the Ontario chapter of the society in March 1983 reported its president’s advice that there was “no need at this moment for any hemophiliac to consider any major changes, either in method of treatment or life style, unless so advised by his treating physician.” In September 1983, members

of the Ontario chapter of the society began to draft a question-and-answer brochure for hemophiliacs about AIDS that included information about sexual relations. The final draft, dated 1 March 1984, contained a recommendation that condoms "could be used" for protection from the transmission of AIDS. The draft was then sent for review to a number of physicians, including members of the medical and scientific advisory committee of the Canadian Hemophilia Society. A revised version of the questions and answers appeared in a special issue about AIDS of *Hemophilia Ontario* that was distributed in late April 1984. No similar publication was available in Canada at the time, and the Ontario chapter did not feel that the national organization was "moving fast enough" in giving advice and information about AIDS to Canadian hemophiliacs. The answer to the question, "Should people with hemophilia continue to have sexual relations with their partners?" read as follows:

AIDS may be transmitted by sexual contact. There has been one case in the U.S. recently where a wife of a hemophiliac AIDS patient developed AIDS herself. This would suggest that wives of hemophiliacs may be at some risk. This possibility is not enough to justify any interruption of normal family relationships where hemophiliacs are in good health.

The published version, unlike the final draft, contained no reference to the use of condoms, or any advice about other precautionary practices, such as the avoidance of sexual relations or the use of other barrier methods, to reduce the risk of sexual transmission of the agent believed to cause AIDS.

By the spring of 1985, despite the rapidly accumulating evidence and the response in the United States, the Canadian Hemophilia Society had not yet provided any guidance to Canadian hemophiliacs about the risk of AIDS associated with sexual relations and measures to prevent its transmission. On 15 March 1985, Dr Robert Card, then the chair of the national society's medical and scientific advisory committee, wrote to his counterpart in Ontario. Part of his letter read as follows:

[T]he Manitoba MSAC [medical and scientific advisory committee] representative has informed me that his MSAC in Manitoba ... will be recommending that barrier methods of birth control be used by all hemophiliac men. Do you agree? Is there evidence in relation to this for the National MSAC to consider a policy?

At a meeting of the medical and scientific advisory council of the society's Ontario chapter eight days later, the chair of the committee referred to recent scientific findings that showed that AIDS was transmitted through sexual contact, but said that the frequency of transmission to heterosexual partners

"remains a question." His remarks prompted a letter from William Mindell, a public health officer in the City of Toronto who was also an active lay member of the Ontario chapter of the Canadian Hemophilia Society. Mr Mindell said, in part:

I was a little disappointed that the MSAC [medical and scientific advisory council] was not willing to discuss a firm statement on sexual relationships between hemophiliacs and their partners. Like it or not, this question will be increasingly asked of treating physicians, nurse coordinators and the CHS [Canadian Hemophilia Society] in phone calls and other inquiries. I think the MSAC ought to provide some guidance on how to answer it.

Mr Mindell enclosed a copy of the article in *The Lancet* of 19 January 1985 that reported the occurrence of AIDS in the infant son of a hemophiliac who had shown signs of the precursor stage of AIDS and that stressed the risk to hemophiliacs and their families.

On 30 March 1985, the Manitoba chapter of the Canadian Hemophilia Society sponsored a medical symposium about AIDS directed primarily to hemophiliacs. Dr Robert Brunham, an infectious disease specialist at the Manitoba Health Sciences Centre and an adviser to physicians treating hemophilia in Manitoba, delivered the opening lecture. A public discussion about safe sex followed between Dr Brunham and the director of a hemophilia treatment centre in another province. Their views reflected the divergence of opinion and incomplete appreciation of the natural history of the disease and of the significance of HIV seropositivity that existed even among experts at that time. Dr Nathan Kobrinsky, who was the director of the hemophilia program at the Health Sciences Centre in Winnipeg and had helped to organize the symposium, testified that the divergent opinions represented "two camps" with "different philosophies of care" that affected "any ultimate decision, be it in terms of product decisions, treatment decisions, recommendations for sexual contact." He said that recommendations that hemophiliacs use condoms and, if HIV-antibody positive, postpone pregnancy were viewed by one of the camps as "conservative but safe" and by the other as "alarmist and extreme."

Dr Brunham's opening remarks included the following summary of knowledge at that time about AIDS and advice to hemophiliacs:

Somewhere between a half and three-quarters of hemophiliacs ... show antibody evidence of exposure.

Additionally ... if you look at the female sex partners of men who have AIDS, about a third of them also have antibody evidence of having been exposed to this virus ...

Now what does it mean to have antibody to the virus? Obviously it means you've been exposed to the virus. And I've told you that this virus causes AIDS, but will everyone who gets exposed to the virus develop AIDS? The answer to that is no. [The] clinical expression of infection with this virus occurs in the minority of individuals ...

But what is important, I think, to note here is that all these individuals who either develop AIDS or ARC [AIDS-related complex, the precursor stage of AIDS] are actively infected with the virus and have the virus present in their blood and other body secretions, and these individuals remain potentially infectious for others ...

Even though ... over half of them remained clinically well, it must in all fairness be said we really don't know what the long term consequences of the infection are ...

This virus demands fairly intensive, intimate, prolonged exposure for transmission to occur ... But, for certain, sexual transmission is important ...

... women who are infected with the virus have the potential to infect their baby during the process of birth and this probably occurs via blood contamination of the baby. So, the major routes of spread are via sex, via blood, and via blood at birth – so called perinatal transmission.

Do we have AIDS in Manitoba hemophiliacs? No we don't. Do we have any evidence that there may have been exposure to the AIDS virus ... in Manitoba? Yes we do ...

Because ... of the potential for sexual spread, I believe it's prudent that seropositive individuals use barrier methods of contraception. Again this would be condom use in men and perhaps foams and diaphragms in women. Whether these are sufficient to guarantee interruption of transmission is uncertain, but their routine use seems reasonable.

For individuals who are seropositive and who are contemplating having children, I think that until we know more about this infection pregnancy should be avoided because of the risk of perinatal transmission to the baby should the mother have been exposed with the virus. Babies appear to be much more susceptible to the full expression of the disease than do adults.

The director of the hemophilia treatment centre questioned the risk of heterosexual transmission of AIDS. He also took issue with some of the precautions proposed by Dr Brunham:

[F]irst of all, not all hemophiliacs are at risk of transmitting the disease through sexual activities. Not all hemophiliacs that are positive for the antibody are likely to transmit the disease and you know, I agree with those recommendations of using condoms or avoiding [pregnancy] ... for a woman who is positive for HTLV-III [HIV] antigen. This is not true for a wife of a hemophiliac who might or might not be positive for HTLV-III. I know that you probably did not intend to say that but, for me as the

treater of hemophiliacs, I feel obliged to reassure my friends they should not avoid having children because they are hemophiliacs and potentially positive for HTLV-III.

For at least some severe hemophiliacs in Manitoba, this debate was the first intimation of the danger of sexual transmission of AIDS and the need to take precautions.

At the next meeting of the Canadian Hemophilia Society's medical and scientific advisory committee, on 19 April 1985, Dr Kobrinsky reported that the Manitoba advisory committee had drafted recommendations for the precautions that should be taken against the sexual transmission of HIV, namely, the use of barrier methods of birth control and consideration of deferral of pregnancy. The national committee then took its first formal position on these matters. The members agreed unanimously that information about the possible role of sexual transmission should be given to hemophiliacs through their treatment centres as quickly as possible and that a carefully worded notice should be prepared for that purpose. A subcommittee, of Dr Kobrinsky, Dr Irwin Walker, and Dr Georges-Étienne Rivard, the last two being physicians treating hemophiliacs in Hamilton and Montreal, respectively, drafted a document that was adopted by the committee for submission to the society's board.

This document, "Status of AIDS and Hemophilia," included the following information:

HTLV-III [HIV] may be transmitted to female sexual partners of hemophiliacs. Two female spouses in the US have developed AIDS and antibodies are occasionally found in the female sexual partners of hemophiliacs. Transmission to newborns also remains a possibility although the risk is unknown. One baby born to the wife of a hemophiliac developed AIDS ...

Many hemophiliacs have HTLV-III in their blood and may have virus in their semen. The specific risk of transmission of AIDS virus by sexual intercourse is unknown, however condoms may prevent this and their use is encouraged. Intercourse through the anus is considered dangerous. The degree of risk to babies born of wives of hemophiliacs is unknown. It presently seems very low but the situation will remain under surveillance. There has been no indication of transference of AIDS through non-sexual contact.

The document was mailed to the executive director of the Canadian Hemophilia Society on 25 April 1985 for distribution to all advisory committee members and hemophilia clinic directors "as rapidly as possible." In a covering letter, Dr Card, as the chair of the advisory committee, said that

because the document contained "new information" about AIDS, hemophilia, and the "relative risk to family members," hemophiliacs "should be made aware of this information expeditiously."

Four months later, in August 1985, the society issued a special "AIDS edition" of its national publication, *Hemophilia Today*, that included information about the risk of sexual and perinatal transmission and the advisory committee's recommendations. In the special issue, condoms were encouraged, anal intercourse discouraged, and hemophiliacs were told that the risk to a fetus was "real" but "remote" and "very small." Hemophiliacs were advised to take any questions they had about AIDS to staff members at their comprehensive-care centres. Not all hemophiliacs were on the national society's mailing list, and some who were did not read the special issue at that time.

The advisory committee's recommendations were published nineteen months after the U.S. National Hemophilia Foundation published its first advisory notice to hemophiliacs about the risk of sexual transmission of AIDS. In his testimony, Dr Card attributed the delay in preparing the recommendations to "some confusion" in the medical reports on the issue in 1984 and to the fact that the medical and scientific advisory committee met only once a year. He also said that "the responsibility for advice lies with the individual physician and treater."

The committee's recommendations were also published by the local chapter of the Canadian Hemophilia Society in several provinces, as was related information about sexual practices. In Ontario, for example, the local chapter's newsletter of July–September 1985 contained an editorial that summarized the recommendations and encouraged the use of condoms. Similar information appeared in the publications of several comprehensive-care clinics during the autumn of 1985. The Hamilton clinic's newsletter of September 1985 encouraged the use of condoms and enclosed an "AIDS Update" distributed by the U.S. National Hemophilia Foundation. The newsletter of the Toronto clinic of November 1985 strongly advised hemophiliacs to use condoms and to limit the number of their partners. Publications distributed by clinics in British Columbia and London, Ontario, also carried information about the sexual transmission of AIDS and necessary preventive measures.

By the end of 1986, most printed material directed to hemophiliacs by the society and the treatment centres contained some message about safe sex. In February 1986, the Canadian Hemophilia Society published a fact sheet called "AIDS and Hemophilia" that included a list of precautions said to "apply to most hemophiliacs whether the [HIV] antibody test is positive or negative." It "strongly recommended" the use of condoms and, because babies "can and have developed AIDS even though the father and mother are healthy," urged the families of hemophiliacs to "avoid pregnancy." More detailed brochures with the same title were produced by the society in collaboration with the Department of National Health and Welfare in early 1987.

They included explicit advice about safe and unsafe sexual activities, detailed instructions about the use of condoms, and explanations about the degree of risk associated with various sexual practices.

Educational material from the federal government

The National Advisory Committee on AIDS, an advisory body to the Department of National Health and Welfare, published several editions of an educational pamphlet for general public distribution called *AIDS in Canada: What You Should Know*. The first edition, issued in the spring of 1984 under the authority of the department, contained the following information:

Almost all cases of AIDS have been found in the following groups:

- Homosexual or bisexual men.
- Intravenous drug users who share needles.
- Immigrants from Haiti.

If you or your sexual partners do not belong to one of these groups your chances of getting AIDS are virtually nil.

It said that AIDS occurred only in "rare cases" among hemophiliacs (two of the total of seventy-four cases reported up to that time in Canada) and answered the question, "How is AIDS spread?" as follows:

The way that AIDS is passed from one person to another is still being investigated. It seems most likely that semen and blood carry the agent. Several methods of transmission have been suggested:

- In homosexual men, anal intercourse appears to be the most likely method of spread.
- A man with AIDS may transmit the disease to his female sexual partner, but this has not occurred in Canada.
- A pregnant woman with AIDS could give the disease to her unborn child.
- A person with hemophilia may get AIDS through the blood products received for blood clotting problems. As of February 1984, two cases of AIDS in Canada have occurred in hemophiliacs.

It recommended: "Do not have sexual relationships with persons known or suspected of having AIDS."

Two hundred thousand copies of the pamphlet were distributed to the Canadian public through supermarkets, health care institutions, and public health educators throughout the country. The pamphlet contained no mention of the use of condoms. According to Dr Alastair Clayton, the director general of the Laboratory Centre for Disease Control, which served as the secretariat

for the National Advisory Committee on AIDS, the committee was instructed not to mention condoms: "When we would put up documentation ... for the deputy minister's office to review," he testified, "it would come down saying, 'Don't mention condoms. Find another way to get the message across.'"

A former member of the committee recalled that there was "profound reluctance to include [the word 'condom'] in such a federal document" because it could offend members of the public. The pamphlet did not alert the sexual partners of hemophiliacs, particularly of hemophiliacs who had developed no indications of AIDS, to the risks they faced or how to reduce those risks.

Contemporary publications of some public-advocacy organizations were far more direct. The AIDS Committee of Toronto, for example, published a monthly bulletin that occasionally addressed the concerns of hemophiliacs. The issue dated February 1984 recommended that hemophiliacs wear condoms as a preventive measure against the transmission of AIDS.

The summer of 1984 saw new evidence that the sexual partners of Canadian hemophiliacs were being exposed to HIV. The initial results from tests of Canadian serum samples for HIV antibody, conducted by the Laboratory Centre for Disease Control, found that one-third of the apparently healthy hemophiliacs who were tested were HIV-antibody positive, and that some apparently healthy wives of HIV-antibody positive hemophiliacs were also HIV-antibody positive. Summaries of the centre's findings were presented in November 1984 at a national public health meeting in Canada and at an international symposium in Anaheim, California. The second edition of the pamphlet *AIDS in Canada: What You Should Know* was distributed to the Canadian public in the spring of 1985. It contained the following information about "Who gets AIDS?":

Of 180 adult patients in Canada (by early 1985), well over half have been homosexual or bisexual men ... [who] probably caught the disease through sexual relationships.

In rare instances, AIDS has occurred in hemophiliacs (two Canadian cases) who may have contracted it through the use of blood products to treat their clotting disorder.

AIDS has also occurred in intravenous drug abusers ...

If you or your sexual partners do not belong to one of these groups, your chances of getting AIDS are virtually zero!

Among the new precautions recommended to "help prevent the spread of AIDS" were the following:

- Decrease your number of different sexual partners and use condoms if you are a male homosexual.
- Do not donate blood if you belong to a group affected by AIDS.

It added: "Remember: AIDS may be contagious before symptoms appear." The committee planned to distribute almost one million copies of the pamphlet by the end of 1985. The only persons told to use condoms were male homosexuals.

It was not until the third edition of the National Advisory Committee on AIDS pamphlet, published in 1986, that everyone at risk was advised to use condoms to prevent transmission of HIV to another person. That pamphlet included the following recommendations:

People infected with the virus may seem completely healthy and may not even know they have it. Everyone should take precautions to protect themselves from becoming infected ...

Know your partner. Use condoms if there is any possibility your partner has been exposed to or is infected with [HIV] ...

Use condoms during sexual intercourse. The proper use of condoms is likely to prevent infection with the virus carried in semen ...

Infected women should use a safe method of contraception to avoid pregnancy until more is known about the risks of transmission from mother to the baby ...

Do not donate blood, organs or sperm.

Responses by the provincial public health authorities

Provincial departments of health did not distribute any materials directed specifically to the spouses and other sexual partners of hemophiliacs. Few public health officials told hemophiliacs and their partners about the ways in which AIDS could be transmitted and about methods to reduce the risk of exposure.

In their testimony in various provinces, public health officials offered several reasons why they had not done more to alert hemophiliacs and their partners to the dangers of sexual and maternal transmission. Some said they had believed that Canadian hemophiliacs were at minimal risk of contracting AIDS because they had thought, mistakenly, that all coagulant blood products used in Canada were manufactured from the plasma of volunteer Canadian donors and that they were therefore safer. In fact, about half the concentrates used in Canada were produced from plasma collected from paid U.S. donors, and products made from Canadian plasma were not necessarily safer. Others said that their departments did not have adequate financial resources to prepare, print, and distribute educational material on the subject. In their efforts to contain the spread of AIDS, some provinces assigned a higher priority to groups other than hemophiliacs and their sexual partners. Dr Michael Rekart, the director of sexually transmitted disease control in British Columbia,

testified that, in 1985, "from a preventive point of view, both from a current point of view and potential future point of view, the epidemic was elsewhere."

In Alberta, Saskatchewan, and Manitoba, public health officials relied on hemophilia treatment clinics to inform the sexual partners of hemophiliacs about how to reduce the risk of infection. Provincial officials in Saskatchewan, Manitoba, and Ontario offered to assist hemophilia treatment clinics in educating hemophiliacs and their sexual partners about the disease, but were told that their help was not needed. Some public health officials were unaware that not all hemophiliacs were affiliated with a hemophilia clinic, and that some obtained their blood products from hospital blood banks and did not visit a specialist in hemophilia treatment for long periods of time.

Little of the educational material prepared by provincial public health officials for the general public contained information alerting the sexual partners of hemophiliacs to their special risks, and in only a few provinces did public health officials circulate material before HIV-antibody testing was introduced in November 1985. In Alberta and Saskatchewan, there were no public education programs organized by the provincial governments about AIDS until 1987. In the materials that were distributed, there was little consistency and there were sometimes important omissions. In some provinces, hemophiliacs were not identified as a high-risk group, nor were their partners described as being at risk. For example, a pamphlet issued by the Department of Health in Newfoundland in 1985 reassured hemophiliacs that, because of the Red Cross's screening of donations for HIV antibody and the introduction of heat-treated factor concentrates, the risk of infection with HIV was "very small"; it did not mention the risk to hemophiliacs of exposure to HIV before those measures were taken, nor did it mention the risk to their sexual partners or encourage them to avoid pregnancy and refrain from donating blood.

In Ontario, some of the public health material did include information about the risk to the sexual partners of hemophiliacs. The Ontario Public Education Panel on AIDS, created by the provincial Ministry of Health in September 1985, produced a number of fact sheets for public distribution. One of the first, "Information about AIDS," distributed in February 1986, described persons who received regular transfusions of blood components or blood products and their sexual partners as being at risk of contracting AIDS. They were advised to abstain from sex or to use condoms. Another of the panel's fact sheets, "Detecting AIDS," distributed in the same month, stated that "people who have received many blood or blood product transfusions since 1980" were in a high-risk group. It recommended HIV testing:

If you are in a high-risk group or have had sex with someone in a high-risk group – even if you don't have symptoms – you may want to be tested for AIDS antibody. This is particularly important if you are considering having a child.

You should not make a blood donation in order to have the test performed. Your doctor can arrange for a test.

The provinces were slow to establish programs to contact the sexual partners of persons diagnosed as having AIDS. These programs are discussed in Chapter 20.

Counselling and therapeutic measures

For most hemophiliacs, the most credible direct source of information about the risks of contracting AIDS, and especially the risks associated with sexual transmission, was not educational pamphlets, brochures, or newsletters but their personal physicians. The printed material distributed by comprehensive-care clinics often suggested that the readers visit their clinic for more detailed and confidential personal counselling.

The nature of the counselling changed as the focus shifted from risk reduction to the management of HIV infection and AIDS. By the end of 1985, heat treatment had eliminated most of the risk of transmission of HIV through factor concentrates. The risk of sexual transmission remained, for by that time most severe type A hemophiliacs were already infected.

The quality and timeliness of the information and advice hemophiliacs received about sexual matters varied according to the clinic and the individual physician. Dr Martin Inwood testified that, from mid-1983, when it became apparent that the syndrome "could well be due to an infectious agent," he advised all his patients at the clinic in London, Ontario, to consider themselves infected until they had evidence to the contrary. Dr Inwood thought the disease should be approached in the same way that hepatitis B was; as a result, members of the clinic staff told patients about the risks of sexual transmission and recommended abstention or the use of condoms. At the Vancouver clinic, Dr Gershon Grove and his colleagues began in 1984 to discuss safe-sex practices with adult patients during their regular visits to the clinic. Many hemophiliacs in Montreal received advice from both their treating physician, Dr Hanna Strawczynski, and an immunologist, Dr Christos Tsoukas, who began studying the spread of AIDS among hemophiliacs and their sexual partners in 1983. Dr Strawczynski testified that she and her colleagues in Montreal began to advise hemophiliacs about sexual precautions in the second half of 1984, two or three months after HIV was discovered. Dr Tsoukas testified that he offered similar counselling to patients enrolled in a nationwide study of hemophiliacs he began in 1984. He explained:

We gave everyone the same kind of counselling whether they tested positive or negative. Because, if you were negative, you still had a risk of sero-converting ... you still had a reason why you should be practising safe sex.

The manner in which counselling services were offered also varied from centre to centre. Frequently the clinic's nurses or social workers conducted the counselling or supplemented that provided by the medical director.

The recollections of hemophilia patients often differed from those of the treating physicians when it came to the timing and quality of their counselling. Many hemophiliacs testified that they did not receive any information about safe sex until after they received the results of their testing for the presence of HIV antibody and were told that they were positive. Most received this information during 1986. Some hemophiliacs first received safe-sex counselling only after the clinic learned that their spouses were pregnant.

The Canadian Hemophilia Clinic Medical Directors Group was created in 1987. At its first meeting, in May of that year, the discussion reflected the need to increase counselling for hemophiliacs and their spouses and the strain this placed on the clinics' resources. The directors discussed making condoms available to their patients through the clinics, but most clinics could not afford the additional expense. It was estimated that 10 to 20 per cent of the spouses of hemophiliacs were already infected with HIV.

By late 1987 and early 1988, most Canadian hemophilia clinics were advising their patients to take preventive measures against the sexual transmission of HIV. The infection of spouses had become known as "the second AIDS epidemic."

Donation of blood by the spouses of hemophiliacs

Some spouses of hemophiliacs regularly donated blood to the Red Cross, often out of gratitude for the life-saving factor concentrates the Red Cross supplied to their husbands. They thus unknowingly contributed to the risk to the blood supply until the Red Cross began the routine testing of blood donations for the presence of HIV antibody in November 1985. By that time, the majority of severe type A hemophiliacs in Canada had probably been infected for between two and three years through the use of factor concentrates.

Many of the sexual partners of hemophiliacs did not know that they were at risk of infection or that they should refrain from donating blood. Those who were infected might not have known their antibody status, even after testing was introduced, because they had not been tested, or had not received their results, or had been tested during the window period of incubation when the antibody could not yet be detected. The Red Cross did not exclude the sexual partners of hemophiliacs from donating blood until January 1986. Dr Roger Perrault, the national director of the blood transfusion service, testified that the Red Cross had assumed that the Canadian Hemophilia Society and the treating physicians were advising the sexual partners of hemophiliacs to refrain from donating blood.

In the spring of 1984, the Red Cross had issued its first pamphlet about AIDS. The pamphlet, *An Important Message to Our Blood Donors*, asked potential donors to refrain from donating if they were members of various high-risk groups. Neither recipients of factor concentrates nor their sexual partners were said to be at high risk. In omitting them, the Red Cross recognized the expressed desire of hemophiliacs and their sexual partners to avoid the stigmatization that came from an association with AIDS.

By the time the Red Cross distributed this first pamphlet, there was strong published evidence of heterosexual transmission of AIDS. Dr Card was then the chair of the Canadian Hemophilia Society's medical and scientific advisory committee, the director of the Saskatoon hemophilia clinic, and a deputy medical director of the Saskatoon blood transfusion centre. In the spring of 1985, he became concerned that neither the Red Cross nor the Canadian Hemophilia Society was alerting the sexual partners of hemophiliacs to the risk involved in their donating blood. In May, Dr Card suggested to the Red Cross that the current pamphlet was ambiguous and that the spouses and other sexual partners of hemophiliacs should be added expressly to the list of high-risk groups. The issue was referred to a meeting on 10 June 1985 of an internal committee of the Red Cross, the donor criteria working group, which rejected the suggestion, recommending that "as hemophiliacs are small in number, their society be advised of the aforementioned risk through Dr Card." In the special AIDS-related issue of *Hemophilia Today* dated August 1985, the editors recommended that "all sexual partners of hemophiliacs refrain from donating blood."

Dr Card continued to object to the Red Cross policy. In late July, he wrote to Dr Brian McSheffrey, the chair of the working group and the medical director of the Saskatoon blood centre, to make it clear that he was concerned about the sexual partners "of all blood product recipients," not only those of hemophiliacs. He also said that the Canadian Hemophilia Society could not reach all the potential donors who might be affected because it did not have a complete list of Canadian hemophiliacs. Dr McSheffrey replied that the subject would be raised at the next meeting of the donor criteria working group. He also suggested to the working group that at its next meeting it consider adding new deferral categories to address Dr Card's objections. In late August 1985, before the group met, a revised pamphlet was circulated to the blood centres. The pamphlet, now called *An Important Message to Our Blood Donors: AIDS*, again did not include the recipients of blood products or their sexual partners among those asked to refrain from donating blood.

Others had also begun to question the Red Cross's policy in this respect. At a meeting of a Red Cross AIDS working group on 24 July 1985, Jane Buchan, the blood donor recruitment area manager of the Toronto blood centre, asked about including the sexual partners of hemophiliacs as a high-risk group. Dr John Derrick, director of the Red Cross AIDS Project, replied that "it was not thought necessary to include this small group in the general information pamphlet"; he said that the subject was to be discussed with

the Canadian Hemophilia Society, which would be notifying its members. Dr Gordon Jessamine, the chief of the field epidemiology division of the Laboratory Centre for Disease Control, attended the next meeting of the group, on 14 August 1985. He raised the same issue and was told that

it was initially felt that while this group is at high risk the group was small and could be educated through the CHS [Canadian Hemophilia Society] not to donate. The chairman of the Medical Advisory Committee of the Canadian Hemophilia Society agrees that sexual partners of hemophiliacs should be included as high risk donors. This recommendation will be taken to the [Red Cross] Donor Criteria Working Group meeting in September.

The minutes of the meeting of the working group in September do not refer to the inclusion of hemophiliacs or their sexual partners in the deferral categories. However, in October 1985 the Red Cross told the Bureau of Biologics that a new pamphlet for potential donors would include hemophiliacs as one of the risk groups, as "requested by the Canadian Haemophiliac Society." In late January 1986, the new pamphlet, which excluded as donors the sexual partners of any person who had "regularly received treatment with blood products," was introduced.

The consequences of sexual transmission

It is not known how many sexual partners of Canadian hemophiliacs became infected as a result of unprotected sex or how many children of these women then became infected, but transmission of both types is known to have occurred. Dr Tsoukas conducted two Canadian studies of the sexual transmission of AIDS to the spouses of hemophiliacs. The first study involved twenty couples who were followed from January 1983 to January 1986. Seventy per cent of the hemophiliacs in that study had symptoms of AIDS or its precursor states, none was practising safe sex, and all but one of their sexual partners were HIV-antibody negative. The study concluded that the risk of transmission of HIV to the sexual partners and family members of symptomatic hemophiliacs was low.

In September 1987, the *Morbidity and Mortality Weekly Report* reported the results of a study of spousal infection in the families of hemophiliacs, conducted jointly by the U.S. Centers for Disease Control and the U.S. National Hemophilia Foundation. Ten per cent of the sexual partners of the hemophiliacs in the study tested positive, and 65 per cent of the children of the seropositive spouses were also HIV-antibody positive.

Dr Tsoukas's second study of spousal infection was conducted in collaboration with Dr Man-Chiu Poon, a physician treating hemophiliacs in Calgary. One of its objectives was to "assess the application and outcome of 'safer

sex' practices in heterosexual couples." The study began in January 1989 and ended in June 1991, during which time it followed fifty-five HIV-seropositive hemophiliacs and their spouses. In a progress report dated October 1989, the investigators wrote that "AIDS cases among the partners of hemophilia patients have been increasing, and the epidemic curve of these heterosexual partners is similar to that of the primary epidemic that was recognized 4 years earlier in the hemophilia population." Three of the women were HIV seropositive as a result of sexual transmission of the virus when they enrolled in the study. Based on U.S. data, one would have expected 7 to 15 per cent of the women to seroconvert during the study period. However, the study was designed to reinforce safe sex and to measure the effectiveness of safe-sex counselling. There were no new HIV seroconversions among the participants in the study.

Commentary

When AIDS first appeared, public health officials understood that there had never been a sexually transmitted disease known to be transmitted homosexually that was not also transmitted heterosexually. The report in the medical literature in January 1984 of a woman infected through sexual intercourse with her asymptomatic hemophiliac spouse confirmed that AIDS would follow the same pattern. In 1984, most Canadian physicians treating hemophiliacs were aware that their hemophiliac patients had cellular immune deficiencies. The occurrence of AIDS in the infant son of a hemophiliac and his spouse, reported in *The Lancet* in January 1985, was evidence that persons who had received factor concentrates might transmit the infectious agent not only to their spouses but also through them to their children.

In Canada, the Canadian Hemophilia Society, its medical and scientific advisory committee, the physicians treating hemophiliacs, and public health officials were aware of the potential risk from AIDS to hemophiliacs and their sexual partners. Despite this knowledge, the response to this risk in Canada was delayed, sporadic, and inconsistent. No advice was given to the national society by its medical and scientific advisory committee until fifteen months after the U.S. National Hemophilia Foundation issued its first advisory notice about AIDS and sexual practices. The information and counselling received by Canadian hemophiliacs from their physicians varied widely, both in content and timeliness. Other groups, most notably the public health authorities and the Red Cross, assumed incorrectly that all hemophiliacs could be reached through the hemophilia organizations and that these organizations and the hemophilia clinics would properly advise the hemophiliacs with whom they were in contact.

The Red Cross did not exclude the sexual partners of hemophiliacs as blood or plasma donors until 1986, partly because it expected the Canadian Hemophilia Society to convey the necessary information to its members.

Not all hemophiliacs were members of the society, nor did all hemophiliacs attend hemophilia clinics. The society's response to the risk was itself tardy and fragmented.

At least some of the occurrences of HIV infection in the sexual partners of hemophiliacs could have been avoided if the couples had received and followed timely safe-sex counselling. The delay in introducing measures to exclude the sexual partners of hemophiliacs from donating blood led to avoidable HIV infections. Investigations conducted by the Red Cross in 1987 discovered that several persons diagnosed as having AIDS had received factor components or cryoprecipitate produced from donations by the infected spouses of hemophiliacs before the introduction of screening for HIV antibody. Some of these persons have since died of AIDS.

The Nature and History of Hepatitis

The threat from AIDS to the safety of the blood supply has overshadowed that from another source – hepatitis. Yet hepatitis has long been recognized as the most common infectious complication of blood transfusions, and before the appearance of HIV and AIDS it was the most serious. The increased use of blood and dried serum during World War II increased awareness of the frequency and seriousness of post-transfusion hepatitis. Recommendations were made during the 1950s for greater efforts to screen out the donors most likely to transmit hepatitis and for more judicious therapeutic use of blood, but for many years hepatitis was considered an acceptable risk of blood transfusion. It was not until the early 1970s, when the first tests for hepatitis B were introduced, that significant reductions were made in the incidence of post-transfusion hepatitis. During the 1980s, although post-transfusion hepatitis remained a substantial risk, attention and research concentrated more on HIV and AIDS. Gradually, the efforts to make blood as free of infectious disease-causing agents as possible returned to hepatitis. The seriousness and extent of post-transfusion hepatitis transmission has only recently been recognized.

The hepatitis viruses

Unlike AIDS, hepatitis is not a new disease. Epidemics of it, most likely of what is now known as hepatitis A, were recorded as early as the 1700s, and perhaps as early as the time of Hippocrates. As with many other diseases, the clinical manifestations were recognized long before the causative agent was identified. Hepatitis was first understood in relation to the most visible symptom it produced, a yellowing of the skin and eyes, called jaundice. By the early twentieth century, jaundice had been linked to liver dysfunction, which has many causes – including viruses, bacteria, drugs, and alcohol abuse. At one time, jaundice was widely believed to be bacterial in origin, but during the 1920s and 1930s investigators began considering a viral cause. After World War II, when methods to detect liver dysfunction were developed, the clinical implications of jaundice became better understood and the term hepatitis – inflammation of the liver – came into use.

The transmission of hepatitis by blood or blood products became a significant concern during World War II. It had occurred long before then, however. In 1883, for example, an epidemic of hepatitis occurred among factory workers in Bremen, Germany, after they had been inoculated with smallpox vaccine. Although it was found that the risk of hepatitis could be reduced by sterilizing the needles used for inoculation, the number of cases of post-inoculation hepatitis grew during the first half of this century with the increased use of vaccines that contained pooled human serum. Perhaps the most serious occurrence involved nearly 30,000 cases of hepatitis that resulted from the use of yellow fever vaccine produced for the U.S. Army in 1941. Smaller outbreaks resulted from vaccination against measles and mumps.

During World War II, large quantities of pooled and dried serum were used on the battlefield. This product had great advantages over whole blood; it was easy to store and could be used without blood typing. However, because it was produced from pools containing many donations, one infectious donor could contaminate an entire lot and cause many cases of hepatitis.

The large wartime incidence of hepatitis provided an opportunity to study the clinical course of the disease. A pattern gradually emerged, suggesting two forms of hepatitis that had similar signs and symptoms but were caused by different agents. One form was transmitted by the fecal-oral route, had a short incubation period, an extremely low fatality rate, and no carrier state. (Carriers of an infectious disease are persons who are free of its symptoms but are infectious and can transmit the disease to others.) The other form had a somewhat longer incubation period, a slightly higher fatality rate, and a distinct carrier state. In 1946, the forms were given the names "infectious" and "serum" hepatitis, respectively, although it was recognized that both agents were in fact infectious. In the 1970s, they were renamed hepatitis A and B.

During the 1960s, an antigen associated with the hepatitis B virus was identified. This identification made possible the development, by the beginning of the 1970s, of a test to identify donated blood contaminated with that virus. Soon after the introduction of the test for hepatitis B it became apparent that, despite a substantial reduction in the incidence of post-transfusion hepatitis, a significant number of cases continued to occur. They were attributed to hepatitis A and to a lack of sensitivity in the test for hepatitis B, which was able to detect only 30 per cent of hepatitis B carriers. A closer examination, however, revealed that many of the cases were epidemiologically different from hepatitis A. Investigators came to believe that a third viral agent was responsible, a hypothesis that was confirmed when a test to detect hepatitis A was developed.

This third form of transfusion-transmitted hepatitis was first described in 1974, and came to be called non-A, non-B hepatitis. It was not called hepatitis C because to do so would have implied the existence of a single causative agent, and it was possible that more than one agent was involved. Although

little was known about the clinical significance of non-A, non-B hepatitis at the time, its incidence among persons who had received blood transfusions was not insignificant. For example, a study at the U.S. National Institutes of Health of 108 open-heart surgery patients, published in 1975, found that twelve of them developed hepatitis. Four of them were subsequently identified as having hepatitis B, and eight were considered to have contracted non-A, non-B hepatitis.

Many cases of what was formerly referred to as non-A, non-B hepatitis are now known to be caused by the hepatitis C virus, or HCV. An antigen associated with HCV was identified in 1989 using molecular biological techniques, but the virus itself has yet to be cultured in the laboratory. There are now known to be several forms of viral hepatitis that have clinical similarities but are caused by different hepatitis viruses. Hepatitis can also be caused by other viruses, such as the Epstein-Barr virus and the cytomegalovirus.

Hepatitis A

The hepatitis A virus (HAV) is a highly infectious virus transmitted by the fecal-oral route. Epidemics spread through contaminated food and water are common, particularly in poorer nations. The incubation period can last from fifteen to forty-five days. Persons infected with hepatitis A develop flu-like symptoms, in most cases followed by jaundice. Symptoms are rare in children but are frequently acute though short-lived in adults. The disease is rarely fatal, and a person who has been infected is immune to reinfection.

Transmission of the hepatitis A virus by blood or blood products is rare. There is no carrier state during which a person is infectious but has no symptoms. The infectious period, during which transmission may occur, lasts between two and six weeks. Nevertheless, transmission by transfusion can occur, and cases resulting from the use of contaminated factor VIII concentrate have recently been documented.

Hepatitis B

The hepatitis B virus (HBV) is transmitted primarily by injection drug use, sexual contact, maternal transfer, and blood transfusion. The disease is endemic in China, southeast Asia, and sub-Sahara Africa, where 5 to 15 per cent of the population may carry the virus. Most infections in these parts of the world are transmitted at the time of birth from mother to child or are acquired during childhood. The prevalence in North America and western Europe is considerably lower; between 0.1 and 1 per cent of the general population are carriers.

Most persons infected with HBV experience acute illness similar to that caused by the hepatitis A virus, although it is frequently more severe and lasts longer. The symptoms include fever, anorexia, malaise, vomiting, and abdominal pain; they may appear at any time between two weeks and six months after infection. Jaundice appears in only 20 to 50 per cent of cases.

All persons infected with HBV are infectious for a time. In most cases, the infection resolves itself. In approximately 5 to 10 per cent of cases, the virus persists for six months or longer. This condition, called chronic hepatitis B, can be free of symptoms and detectable only by laboratory results; progression of the disease is slow but its results range from mild inflammation of the liver to cirrhosis and liver cancer. Persons who develop chronic hepatitis remain infectious, and a significant number are symptom-free. As a result of this potentially lengthy carrier state, HBV is readily transmitted by transfusion because blood donors may not recognize that they are infected. Transmission by this route has been nearly eradicated through the use of various tests to screen blood donations.

Hepatitis B is endemic in certain regions of the world, and as a result liver cancer associated with HBV infection is one of the world's most common fatal malignancies.

Hepatitis C

Acute illness caused by the hepatitis C virus (HCV) is less common and less severe than that caused by HBV. The incubation period normally lasts from fifteen to 150 days. Only 25 per cent of infections result in jaundice. As many as 90 per cent become chronic. As in hepatitis B, the chronically infected may be symptom-free carriers without any liver disease. Knowledge of the long-term consequences of hepatitis C is still evolving, but it appears that 10 per cent of chronic infections result in cirrhosis or liver cancer after ten years. That proportion increases to 20 per cent after twenty years. The fact that HCV can remain in the body for long periods of time without appearing to cause serious effects led early investigators to conclude that it was a benign infection.

Like HBV, HCV is transmissible by blood. The most common means of transmission is through the sharing of needles by drug users. Because of the symptom-free carrier state, it can be transmitted through the blood supply if donors are unaware of their condition. However, testing has greatly reduced transmission by this route.

Other hepatitis viruses

Two other hepatitis viruses are known to be transmissible by blood transfusion, and a third can in theory be transmitted in this manner. The hepatitis D virus (HDV), which causes delta hepatitis, needs the protein that is found on the outer shell of the hepatitis B virus for transmission. Accordingly, HDV is found only in persons infected with HBV, and the disease is most common in persons with chronic HBV infection. In North America and western Europe, HDV occurs most frequently in hemophiliacs, intravenous drug users, and recipients of many transfusions. More than 70 per cent of these HDV infections progress to chronic delta hepatitis. Delta hepatitis is more severe than hepatitis B; estimates of the mortality rate range between 2 and 20 per cent. One study found that 60 to 70 per cent of patients with chronic HDV infection

eventually developed cirrhosis, and most of them died. Although cirrhosis usually occurred between ten and fifteen years after infection, in some cases it occurred after only two years. HDV infection usually resolves at the same time as the HBV infection that accompanied it.

The hepatitis E virus (HEV) is epidemiologically similar to HAV in that it is most commonly transmitted by the fecal-oral route, but it may also be transmissible through blood. It was recognized in the early 1980s when large outbreaks of non-A, non-B hepatitis occurred in populations already immune to the hepatitis A virus. Like HAV it does not lead to chronic disease or a carrier state. Although epidemics have been observed in Asia, parts of Africa, and parts of Central and South America, none has occurred recently in North America or western Europe. No cases of transmission by blood or blood products have thus far been observed.

The hepatitis G virus (HGV), identified only in 1995, is transmissible by blood transfusion and has been shown to be present in as many as 1 to 2 per cent of blood donors in the United States. Its prevalence among Canadian blood donors is unknown. Little is known about the extent to which HGV causes chronic hepatitis and cirrhosis, and study of it continues. Researchers originally believed HGV to be responsible for hepatitis that was not attributable to the hepatitis viruses A through E, but two recent studies have concluded that there is no evidence that HGV causes hepatitis at all.

Testing for hepatitis B infection

In 1968, researchers discovered that a previously known antigen was associated with hepatitis B; its presence in a person's blood indicated that he or she was infected with the hepatitis B virus and could transmit the infection to others. This structure came to be called the hepatitis B surface antigen (HBsAg). The subsequent development of a test to detect the presence of HBsAg in blood proved to be a valuable screening tool against the spread of hepatitis B through transfusion. That test was introduced in Canada in 1971 and by early the next year was fully implemented in all blood centres operated by the Canadian Red Cross Society (Red Cross).

An understanding of the basis of the tests devised for detecting the presence of the hepatitis B virus, and of the processes by which that virus reproduces and causes infection, is essential to an understanding of the debate that eventually occurred over possible measures to screen donations for the virus that causes hepatitis C. When a virus enters the body of a person, it is recognized as foreign and stimulates an immune response. In the case of the hepatitis B virus, the body first recognizes the molecular structures on the surface of the virus that have come to be called hepatitis B surface antigens. The body responds by producing antibodies (anti-HBs) that react specifically with the surface antigens. These antibodies are often effective in combating the infection and clearing the virus from the body. The immune response, involving antigens and antibodies, is discussed in greater detail in Chapter 2.

To cause infection, the hepatitis B virus needs to reproduce. It does this by entering the body's cells and instructing them to make many copies of itself. The newly formed viruses then are released and go on to infect more cells. This process causes inflammation and may eventually lead to liver disease. In the process of instructing the body's cells to produce new copies, the infecting virus breaks down into a surface coating and a core. If the virus is likened to an orange, the surface coating of the virus is the peel of the orange, the core is the seeds, and replication involves peeling the orange to expose the seeds. Once the core is exposed, the host body recognizes on it another form of molecular structure, called a core antigen (HBc). The body responds by forming antibodies to the core antigen. Core antibodies (anti-HBc) are usually detectable between three and five weeks after exposure to the virus.

Although the core is essential for the reproductive process, it alone cannot cause infection. Only the entire virus can. As a result, the presence of hepatitis B surface antigens indicates the presence of the infective virus. They can be detected at any time between one and twelve weeks after the virus first enters the body. If the antibodies to the surface antigens are effective in clearing the virus, the infection resolves and the surface antigens are no longer detectable. The antibodies to the surface antigen may, however, remain in the body for many years, even for life, and can protect persons from subsequent hepatitis B infections. The antibodies to the core antigen also remain after infection and, although not protective, can be used as an indicator or marker of past hepatitis B infection.

Regulations to reduce the risk of transmission through blood

When testing for hepatitis B was introduced, much of the blood supply in the United States came from paid donors. The tests confirmed what blood bankers in the United States had known since the late 1950s, that blood that was paid for was associated with a significantly increased risk of transmitting hepatitis. In a study conducted at the U.S. National Institutes of Health, researchers estimated that, had blood from paid donors been excluded from the system before the introduction of testing for hepatitis B surface antigen, post-transfusion hepatitis would have been reduced by 70 per cent.

Regulations in the United States have prohibited taking blood from persons with a history of hepatitis since the 1950s, but have never prohibited the use of blood for which the donors were paid. In 1978, however, the Food and Drug Administration required that the label on every blood bag state whether the contents came from a volunteer donor or from a person who had been paid. Because components derived from paid blood donations were known to have a greater risk of transmitting hepatitis, hospitals and physicians were reluctant to use them because of their concern about liability. Today nearly all the components used for transfusion in the United States come from

volunteer donations. There are occasional exceptions, as at the Mayo Clinic in Rochester, Minnesota, which uses blood purchased from a group of donors who are well screened and known to present no greater risk of infection than volunteer donors. The percentage of whole blood collected from paid donors decreased from 11 per cent in 1971 to 2.2 per cent in 1980. Plasma collected by plasmapheresis for processing into blood products by the commercial fractionation industry is, however, still obtained primarily from paid donors in the United States.

Testing for the hepatitis B surface antigen also revealed an increased risk of hepatitis transmission in blood obtained from prison inmates. In the United States, inmates received incentives, such as free cigarettes, if they donated blood. Despite the known high prevalence of hepatitis in prisons, the inmates represented a reliable source of blood donations, and blood collection agencies continued to use them. That practice declined only when it was found that inmates were also at increased risk of contracting and transmitting HIV. The collection of blood from prison inmates has never been prohibited in the United States by regulation, and at least one pharmaceutical manufacturer was known to be accepting plasma collected at prisons as recently as the early 1990s.

Canada, with some exceptions, has always relied on volunteer donors. Although it has never paid its donors, the Red Cross has collected donations from prison inmates. This practice was discontinued in 1971, after the hepatitis B surface antigen test demonstrated conclusively that prison inmates had a significantly higher prevalence of hepatitis than the rest of the population. The decision was made as a matter of Red Cross policy and not in response to regulation.

In Canada, since the early 1940s, the *Regulations to the Food and Drugs Act* pertaining to "Preparations from Human Sources" have required that human plasma and serum used in the preparation of certain drugs, listed in Schedule D of the *Act*, not be obtained from anyone who has not been certified to be healthy or who has a history of a disease transmissible by blood transfusion. Members of the Bureau of Biologics, the bureau of the Health Protection Branch of the Department of National Health and Welfare that regulates biological drugs including blood products, testified that, although this wording was not changed after a test for hepatitis B became available, it was interpreted to mean infectivity at the time of donation as indicated by tests for the hepatitis B surface antigen.

From November 1978, the *Food and Drug Regulations* have included "human plasma collected by plasmapheresis." One of the principal reasons for the addition was to prevent the widespread transmission of hepatitis through blood products derived from pooled plasma. The *Regulations* stipulate that plasma collected for the manufacture of blood products be obtained from donors who are free of any disease transmissible by blood transfusion, who have no history of viral hepatitis or close contact with another person with a

history of viral hepatitis within the previous six months, who have not received a blood product that could be a source of viral hepatitis, and whose plasma did not react to an acceptable test for the hepatitis B antigen.

It is the position of the Government of Canada and the evidence of representatives of the Bureau of Biologics that, until 1978, the bureau had no regulatory authority over the Red Cross. The *Regulations* that governed "Preparations from Human Sources" applied only to "sera and drugs analogous thereto" and to "blood derivatives," and these categories were not interpreted to include blood components, such as whole blood, red cells, white cells, platelets, or plasma collected by the Red Cross. Moreover, the *Regulations* applied only to manufacturers of blood products, and the Red Cross was not a manufacturer at that time. After 1978, when plasma collected by plasma-pheresis was added to Schedule D, the bureau's regulatory control extended only to that aspect of the Red Cross's blood collections. Blood components for transfusion were not added to Schedule D until 1989. Thus, although it was a standard of practice, there was no regulatory requirement that blood components intended for transfusion be tested for the hepatitis B surface antigen.

A detailed consideration of the *Food and Drugs Act*, and its *Regulations*, and of the Bureau of Biologics' interpretation of its role and responsibilities appears in Chapter 6.

Transmission of hepatitis through blood products

Post-transfusion hepatitis B continued to be common among users of blood products, including hemophiliacs, even after the introduction of testing for the surface antigen. Even in the absence of a specific test, it was gradually recognized that non-A, non-B hepatitis was also appearing among hemophiliacs. The factor concentrates on which hemophiliacs depended were manufactured from pooled plasma and thus were almost certain to expose their users to the risk of hepatitis, at least until the manufacturers began using techniques to inactivate the virus in the mid-1980s.

The transmission of hepatitis was accepted as an unavoidable risk in the treatment of hemophilia. Before factor concentrates became widely available in the late 1970s, severe hemophiliacs used so many units of plasma, and later cryoprecipitate, that the probability of exposure to hepatitis was extremely high. The use of concentrates made exposure a near certainty, because their manufacture required the pooling of thousands of units and even one infected unit could contaminate an entire manufacturer's lot. Even this risk was considered acceptable when weighed against the enormous benefits of using concentrates.

The problem of balancing risk and benefit in using factor concentrates was discussed at a meeting of representatives of the Red Cross and the Bureau of Biologics on 13 July 1981. During it, Dr John Derrick, the Red Cross's director of operational research, described the Red Cross's record-keeping system and

its procedures in tracing blood component units to donors. Because some of the units were traced to donors whose plasma had been used to make blood products, a number of lots of fractionated blood products were withheld from distribution, pending a review by the bureau and the Red Cross. The practice of the Red Cross at that time was to distribute blood products if a suspect donation had already been pooled with other units of plasma and the loss of that pool of plasma was expected to have "the potential of seriously affecting" the delivery of plasma fractionation products. It was agreed at the meeting of 13 July that, when a lot was thought to contain an implicated unit, the bureau would be notified and each situation would be resolved individually, using a "benefit/risk ratio":

there comes a point where a decision has to be made as to which possibility:

- the removal of possibly contaminated fractionation products from distribution, or
- their loss as therapeutic agents (e.g. Factor VIII concentrate),

constitutes the greater threat to the well being of the individuals requiring them, i.e. the benefit/risk ratio.

The Red Cross said that, in the absence of a specific test for non-A, non-B hepatitis, it would make every effort to trace implicated donors for both blood components and blood products. The policy reached at the meeting did not provide for any information to be sent to physicians or hemophiliacs about the increased risk of hepatitis associated with a particular suspect lot of factor concentrate. The product would be released and distributed in the normal manner.

As a consequence, factor concentrates were not always destroyed or recalled when it was learned that some of the plasma from which they were derived came from persons who subsequently tested positive for hepatitis B. Instead, depending on the quantity of factor concentrates available or being manufactured at the time, they might be distributed for use by hemophiliacs. This policy, of permitting the distribution of factor concentrates known to contain plasma from hepatitis-positive donors when stocks of the product were low, was affirmed in July 1985 and again in 1987.

Reporting and the incidence of post-transfusion hepatitis

Data based on the reporting of infectious diseases by physicians are notoriously unreliable, and those for hepatitis are particularly undependable because the nature of the disease makes it difficult to detect. With respect to post-transfusion hepatitis, although patients who receive transfusions are likely to be in hospital for several days, the incubation period preceding the appearance of symptoms may be long, and in a significant percentage of cases symptoms do not develop. As a result, patients are often discharged

without any recognition of the infection. Hepatitis reporting accordingly requires special diligence. Reporting of post-transfusion hepatitis B became less important as testing methods improved and the incidence decreased, but that did not reduce the need for reporting post-transfusion non-A, non-B hepatitis, for which no specific test was available until 1990.

By the early 1970s, in most provinces, physicians were required by provincial regulations to report cases of hepatitis A and hepatitis B, and by the late 1970s some provinces had amended their lists of notifiable diseases to include "hepatitis unspecified" or "hepatitis other" – references to what was becoming known as non-A, non-B hepatitis. Despite these regulations, it was generally recognized that occurrences of hepatitis were significantly underreported. The information collected by the provinces was tabulated nationally by the Bureau of Epidemiology of the Laboratory Centre for Disease Control, the federal agency responsible for disease surveillance. Non-A, non-B hepatitis was not added to the national tabulations until July 1982, when it was described as "hepatitis other and unspecified viral." The centre had no means of requiring physicians to report the occurrence of disease directly to it, however. In 1983, the first year for which the collected data for non-A, non-B hepatitis were published, there were 134 reported cases. The numbers rose to 171 in 1984 and 230 in 1985. By 1995, the total number of reported cases of what was by then called hepatitis C exceeded 10,000. In all likelihood, the large increase reflected the introduction of testing for HCV antibody rather than a substantial increase in prevalence.

In addition to the under-reporting of occurrences, little or no information was collected by the provinces or the Laboratory Centre for Disease Control about the causes of the infections that were reported. In particular, there was no information about the proportion of reported cases that was related to transfusions or the use of blood products. The Red Cross was required to notify provincial health authorities when a blood donor tested positive for hepatitis B, but that notification was not done routinely by all blood centres and, at least until the 1980s, most blood centres notified only the donor's physician. The physician might or might not report the case to the public health authorities.

No studies were conducted of the incidence of post-transfusion hepatitis (the rate of occurrence within a given population) in Canada during the 1960s and 1970s. The introduction of hepatitis B surface antigen testing of blood donations in 1971 and 1972 did, however, produce data about the presence of the antigen in blood donors. In a study published in the *Canadian Medical Association Journal* in 1973, the authors analysed data from the Red Cross's Toronto blood centre, where testing had been introduced in April 1971. There, 0.15 per cent of donations tested positive. This was a significant rate, equal to or greater than that found among volunteer donors in the United States. Using those data, the authors calculated how many cases of post-transfusion

hepatitis might have been expected in Toronto in 1969, before testing began. They estimated that number as 242. They further estimated that, assuming that only those cases in which jaundice developed would be reported, there would be at least sixty reported cases of post-transfusion hepatitis in Toronto that year. Only fifteen reports had been received. They concluded that, in general, only one-quarter of the minimum expected number of reported cases of post-transfusion hepatitis were in fact reported.

Accurate information about the incidence of post-transfusion hepatitis in Canada clearly was needed, but it could not be obtained by extrapolating from the number of reported cases. The investigators therefore proposed a prospective study, in which a group of patients who were going to receive transfusions would be closely monitored for any post-transfusion development of hepatitis, with or without jaundice. The information to be obtained included the true incidence of icteric (producing jaundice) and non-icteric hepatitis B related to blood transfusion, the frequency of post-transfusion jaundice resulting from causes other than hepatitis B, and the risk of hepatitis in blood that had reacted negatively to a test for the hepatitis B antigen.

In April 1975, the Red Cross's national scientific advisory committee (the predecessor of the blood transfusion service advisory committee) discussed the need for better information about the efficacy of testing for hepatitis B in reducing post-transfusion hepatitis. It was pointed out that the incidence of post-transfusion hepatitis was unknown for the periods before and after hepatitis B surface antigen testing was introduced. It was agreed that such information was highly desirable, and the hope was expressed that interested parties might work together to devise a surveillance program. No study or surveillance was undertaken.

The number of blood donors who tested positive for hepatitis B continued to be extremely high in certain areas of Canada. In Red Cross data from May 1973 to August 1974, the proportion of first-time donors testing positive ranged from 0.114 per cent in the Maritimes to 0.405 per cent in Quebec. For repeat donors the proportion ranged from 0.017 per cent in Saskatchewan to 0.242 per cent in Quebec. Those data were reported in the *Canadian Medical Association Journal* in January 1975 by Dr Brian Moore, the director of the Red Cross's national reference laboratory, and Dr Roger Perrault, the national director of the Red Cross's blood transfusion service. They concluded:

The effectiveness of our screening program for HBsAg [the hepatitis B surface antigen] in blood donors is difficult to assess because, although viral hepatitis is a notifiable disease, the reporting of post-transfusion hepatitis (PTH) leaves much to be desired. Hepatitis B infection may have an incubation period of up to 180 days; thus, it is easy to miss the connection between an earlier transfusion and the present infection.

They appealed, with particular emphasis, to Canadian physicians for information about post-transfusion hepatitis:

We therefore ask every physician to report to his or her nearest regional transfusion centre any patient with suspected viral hepatitis with a history of having received a transfusion of blood or blood products in the previous 6 months.

Little more was done at the national level until 1981 to improve the reporting of post-transfusion hepatitis by physicians to the Red Cross.

The need for better information was not confined to Canada. In May 1982, it was discussed by the Council of Europe's committee of experts on blood transfusion and immunoematology at a meeting in Ottawa, in which the Canadian Red Cross participated. The committee concluded that

[i]n most member states, data on the incidence of post-transfusion infections are inadequate. There is great need for stricter epidemiological monitoring of infectious diseases in general, as well as for prospective studies on post-transfusion infections by country as well as by blood product and origin.

Even less was known about the incidence of post-transfusion non-A, non-B hepatitis in Canada than about the incidence of post-transfusion hepatitis B. More was known about the incidence of post-transfusion non-A, non-B hepatitis in the United States, where the original research that had led to the recognition of non-A, non-B hepatitis had been conducted. U.S. data were reported at a meeting of the Canadian Red Cross's blood transfusion service advisory committee on 29 November 1978, at which Dr Lewellys Barker, the vice-president of health services of the American Red Cross, spoke. His comments were summarized in the minutes of the meeting:

The outlook was not terribly promising with reference to identifying the agent virus, or whatever it may be. He saw lots of work ahead on non-specific methods ...

[A member] asked if there was any evidence of Non-A, Non-B infections from the transfusion of BTS [blood transfusion service] blood products. Figures for Canada were not available, but Dr Barker reported that in the U.S. attack rate is between 5 and 10 percent in several centres using volunteer blood, ninety percent of them being Non-A, Non-B.

Although the corresponding incidence rate for Canada was then unknown, a rate of 5 to 10 per cent was acknowledged subsequently to be a matter of serious concern to the Red Cross.

The need for more complete data was again recognized in mid-1981, this time by the hepatitis working group, an internal Red Cross body drawn from the blood transfusion service. Dr Martin Davey, the assistant national

director of the blood transfusion service and a member of the working group, sent all hospitals that received blood from the Red Cross a circular "concerning the reporting of hepatitis cases following and possibly related to transfusion." This, the minutes of the working group record, brought about "an increasing number of telephone and written reports" of post-transfusion hepatitis from physicians.

Two years after Dr Davey's circular, however, there were still no adequate data on the incidence of transfusion-associated hepatitis in Canada. In July 1983, the hepatitis working group agreed that any number quoted would be extremely "brittle" because it would be based on reported cases only. One of the committee members "felt" that cases of transfusion-associated hepatitis reported to the Toronto blood centre amounted to an incidence of one in every 10,000 units transfused or, since most patients received more than one unit, one in every 3,000 patients who received transfusions.

The working group tried unsuccessfully to develop a national form designed specifically for the reporting of post-transfusion hepatitis. The Red Cross had a general reporting form that could be used for all adverse reactions, but it was not used uniformly by the blood centres, and some blood centres had developed their own reporting forms. In July 1981, the working group identified the clinical and laboratory information that should be requested in a standard national form, including the presence of jaundice and the level of alanine amino transferase (ALT) in the recipient's blood. An elevated ALT level is an indicator of liver dysfunction. A procedure was devised under which the medical director of every blood centre would be directly responsible for ensuring that the form, including information about both the patient and the donor, was completed as fully as possible and forwarded to the director of medical services at the Red Cross national office. A draft was presented by Dr Davey to the medical directors when they met in October 1981, but it was not adopted by them for national use.

Despite continuing efforts by the working group, the Red Cross never adopted a national reporting form specifically for post-transfusion hepatitis. At a meeting of the hepatitis working group on 14 July 1983, Dr Davey said that either of the forms used by the Toronto and Vancouver centres would be satisfactory for use by other centres. At a meeting on 28 October 1983, it was reported that a "hepatitis report form package" had been sent to the blood centres. By February 1985, efforts were again being made to "standardize the format for reporting transfusion-associated incidents," and draft forms were to be circulated to hospitals for comments. Although these efforts were primarily for hepatitis, a uniform system for the reporting of all transfusion-associated infections was being proposed. It was not until testing for HIV antibody was implemented during the autumn of 1985 that a single standard national procedure and form were developed for transfusion-related infections, including AIDS and hepatitis.

Throughout the period 1981–5, the reporting to the Red Cross of cases of post-transfusion hepatitis was sporadic and incomplete. The hepatitis working group commented on 13 February 1985:

More cases of post-transfusion hepatitis are reported from some centres than from others. This probably represents a greater willingness to report rather than a greater incidence of post-transfusion hepatitis in the local population. More effort should be put into getting reports. Hospitals need to be sensitised to the need to report by the area medical directors.

The inadequacy of reporting persisted throughout the 1980s. The lack of information about the incidence in Canada of post-transfusion non-A, non-B hepatitis – and of post-transfusion hepatitis generally – hindered the policy makers in the Canadian blood system as they considered measures that might reduce the risk of infection.

Donor deferral

The Red Cross has long had a policy of deferring donors, that is, of asking prospective donors not to give blood, either permanently or temporarily, if taking a donation would represent a threat to the health of the donor, or if using a donation would pose a threat to a recipient. Since the 1940s, it has deferred persons with a history of hepatitis. Before the development of a specific test for hepatitis B, it could do so only by questioning prospective donors. Those who reported a history of jaundice were deferred permanently, and those who reported a recent contact with someone with hepatitis were deferred for six months. After the Red Cross began testing donations for the hepatitis B surface antigen in 1971, donors who tested positive were excluded permanently.

The testing and questioning could not identify all blood donors capable of transmitting hepatitis, however, and post-transfusion hepatitis continued to occur even after testing for hepatitis B was introduced. When the Red Cross received a report of post-transfusion hepatitis, it tried to trace the donation or donations used and to identify the donor or donors involved. In cases involving hepatitis B, donors could be tested and, in most cases, it was possible to identify those whose donations were responsible for the transmission of hepatitis. Those donors were said to be “implicated” in the transmission of post-transfusion hepatitis. Donors identified in this manner who tested positive for hepatitis B were permanently excluded from donating.

In the absence of a specific test for non-A, non-B hepatitis, no similar procedure could be used to defer donors implicated in the transmission of that disease. Blood bankers instead placed great reliance on questioning prospective blood donors in order to exclude those who seemed likely to transmit non-A, non-B hepatitis. Another means available was to develop a system for tracing

and deferring donors who might be implicated in a case of post-transfusion non-A, non-B hepatitis. Because the reporting of post-transfusion non-A, non-B hepatitis was even less reliable than the reporting of hepatitis B, any such system would necessarily be limited in its effectiveness. Without such a system, however, it would be possible for a regular blood donor to transmit non-A, non-B hepatitis to recipients of transfusions without the donor, the recipients, or the Red Cross realizing it for many years, if ever. The major challenge in developing such a system was to determine when, in the absence of a specific test, a donor should be considered to be implicated. This determination was not difficult if the infected recipient had received a blood component from only one donor, but often many donors were involved in a single case and all of the units were then viewed as "possibly implicated."

The issue of donor deferral was raised by Dr Moore, the director of the Red Cross national reference laboratory, in a memorandum dated 19 May 1981. Dr Moore proposed that ALT testing be used to help determine whether a donor was implicated in the transmission of non-A, non-B hepatitis. He suggested that test results above 2.25 SD (standard deviation) should be considered positive and the donor considered a "probable" cause of transfusion-transmitted hepatitis. In his view, this was the only legitimate use for ALT at that time.

The hepatitis working group, an internal committee of the Red Cross, endorsed Dr Moore's proposal at a meeting on 8 July 1981. It agreed that all donors possibly implicated in a case of post-transfusion hepatitis should be identified, traced, and recalled for testing, and that the donors' testing records and the disposition of all components derived from their donations should be checked. All donors found to be "HBsAg or antibody positive," or who had impaired liver function as evidenced by two elevated ALT tests four weeks apart, were to be treated as implicated. They were to be referred to their physicians and rejected as donors in the future.

When the medical directors of the Red Cross blood transfusion service met in October 1981, they did not approve the procedure proposed by Dr Moore and endorsed by the hepatitis working group. Instead they decided that the exclusion of any donor because of the possible transmission of hepatitis should be at the discretion of the medical director of the local blood centre. Their revision allowed the medical director to decide, if a patient had received many units in transfusion, that testing all the donors possibly implicated was too onerous a task. The donors possibly implicated would not be traced or tested for levels of ALT or the presence of the hepatitis B surface antigen.

Any donor who was implicated in a case of post-transfusion hepatitis B, but who was not traced and tested, might still be identified and deferred as a result of routine testing of blood donations on the next occasion that he or she donated blood. This was not true for donors implicated in the transmission of non-A, non-B hepatitis, as long as there was no routine testing for that

disease. To increase the likelihood of identifying potential carriers of non-A, non-B hepatitis, the Toronto blood centre established a registry of all possibly implicated donors and it excluded any donor who appeared on it twice. At its meeting on 5 February 1982, the hepatitis working group recommended that other centres establish similar registries. It also considered the need for a national registry that would track donors identified as possibly implicated in the transmission of post-transfusion hepatitis by any of the seventeen Red Cross blood centres. As late as June 1984, a system had still not been developed, although the minutes of the hepatitis working group record that a system for tracking implicated donors in post-transfusion hepatitis cases was being established. In fact, a national registry of donors implicated in non-A, non-B hepatitis was never developed.

Surrogate Testing

A surrogate is a substitute – something or someone taking the place of another. In the context of blood safety, surrogate tests are used to detect viruses for which no specific test exists and to supplement specific tests that are insufficiently sensitive. Two principal kinds of surrogate tests are used to identify infected blood donations. The first identifies the presence of a condition found to be associated with a donor's infection. One such test measures the level of alanine amino transferase (ALT) in a donor's blood; levels significantly above normal indicate liver dysfunction, possibly caused by a hepatitis virus. The second kind tests for the presence of a marker of infection with a virus that is not the one of real concern but that is epidemiologically similar. An example is a test that detects the antibody to the hepatitis B core antigen (anti-HBc), an indicator of previous hepatitis B infection. The test has been used as a surrogate test for non-A, non-B hepatitis and for HIV and AIDS. Its use in this manner is based on similarities in the means by which the diseases are transmitted and on the reasonable expectation that a person who has been exposed to hepatitis B is more than normally likely to have been exposed to non-A, non-B hepatitis or to HIV and AIDS, or both.

Surrogate tests are rarely, if ever, perfect substitutes for specific tests. Because they are imperfect, controversy arises over both their use and any failure to use them. Because they lack sensitivity and specificity, it is difficult to determine with certainty their effectiveness in identifying blood donations that should be excluded, the number of donors that might be excluded unnecessarily, and the explanation that should be given to donors whose blood is rejected. These types of issues arose in the debates that occurred during the 1980s over the use of surrogate tests to reduce the risk of contamination of the blood supply with non-A, non-B hepatitis.

ALT as a surrogate test

The use of surrogate markers for hepatitis was investigated before a specific test for hepatitis B was developed in the early 1970s. During the 1950s, the presence of certain enzymes above normal levels was used to assess liver function, and it was thought they could also be used to diagnose hepatitis. As

early as 1954, it was suggested in the medical literature that post-transfusion hepatitis might be reduced by using tests for those enzymes to screen prospective blood donors. However, these early liver function tests proved disappointing as surrogate tests for hepatitis because of inconsistent results and a variety of technical problems.

By the late 1950s, simple methods had been developed for measuring the level of alanine amino transferase (ALT) in serum. ALT is one of several enzymes that speed the transfer of an amino group from an amino acid to a carbohydrate. This process is known as transamination and, although it occurs in other human tissues, it occurs principally in the liver. When there is extensive damage to the liver, the enzymes are released into the blood stream and the enzyme levels there are elevated. The level found in serum can therefore be used as a marker of liver dysfunction. Early studies failed to demonstrate consistently the usefulness of ALT testing in screening blood donations, however, and interest in ALT as a surrogate test diminished after the development of the first specific tests for hepatitis B. It was not until the mid-1970s, when it became apparent that a third form of viral hepatitis existed, that interest revived in ALT as a surrogate test.

The levels of ALT and other enzymes continued to be used to diagnose liver dysfunction caused by hepatitis viruses. Even today an elevated ALT, in the absence of some other medical explanation, is used to support a diagnosis of hepatitis.

The transfusion transmitted viruses (TTV) study

The high rate of post-transfusion hepatitis that continued to occur in the United States, even after the introduction of a specific test for hepatitis B, prompted the National Heart, Lung, and Blood Institute (one of the U.S. National Institutes of Health) to pay for a study that would assess the incidence and cause of post-transfusion viral hepatitis and evaluate methods of reducing its risk. This transfusion transmitted virus (TTV) study was designed when residual cases of post-transfusion hepatitis were still attributed solely to the insensitivity of the early test for the hepatitis B surface antigen. One of the study's primary objectives was to evaluate the efficacy of various methods of testing for hepatitis B. By the time the study began in July 1974, however, the improvement in hepatitis B testing and the development of a test for hepatitis A had made it clear that at least one more hepatitis virus existed. Non-A, non-B hepatitis then became the focus of the study.

Four centres participated in the TTV study, which examined the incidence of hepatitis in patients who received transfusions and in a control group of patients who had no need for transfusions. It was a prospective study; it began before any of the patients received transfusions and followed them to see who developed hepatitis. Two of the centres, in St Louis and New York, used only blood donated by volunteers. A third centre, in Los Angeles, used blood from both volunteer and paid donors. The fourth, in Houston, used blood donated

by families and friends of hospitalized patients. The study excluded patients, whether or not they received transfusions, who had a history of chronic liver disease, took medications that might affect liver function, had a history of jaundice or hepatitis or occupational exposure to hepatitis, or had received a transfusion in the preceding twelve months. Blood samples were taken from all patients before they received a transfusion, and only patients with normal ALT levels were enrolled in the study. Subsequent samples were taken at two-week intervals for the first three months, at three-week intervals for the next three months, and again at ten months. All centres used the same methods and materials. A diagnosis of hepatitis was made if, within fourteen to 180 days after the transfusion, two sequential samples had ALT levels above normal, that is, equal to or greater than 45 IUs (international units), and no other probable cause was identified. At least one of the two samples had to have an ALT level twice the upper limit of normal, that is, equal to or greater than 90 IUs. Patients who were diagnosed with hepatitis, but who did not test positive for hepatitis A or hepatitis B, were classified as having non-A, non-B hepatitis.

The data from the TTV study were analysed and published in two stages. The first stage was concerned with the efficacy of ALT as a surrogate test for non-A, non-B hepatitis. The second stage examined the efficacy of testing for the presence of anti-HBc (the antibody to the hepatitis B core antigen) as a surrogate test for non-A, non-B hepatitis.

The preliminary results related to ALT, published as abstracts in 1975 and more fully in 1978, suggested an association between elevated ALT levels in donors and the occurrence of non-A, non-B hepatitis in recipients. The final results, published in the *New England Journal of Medicine* in April 1981, confirmed that association – the higher the ALT level in the donor, the more likely hepatitis occurred in the recipient. The study was based on 1,513 patients who had received blood from 5,564 donors between 1974 and 1979. In the entire group, 10 per cent of the recipients of transfusions developed post-transfusion hepatitis. Among the donors who had ALT levels of from 45 to 59 IUs, 35 per cent were associated with the development of post-transfusion non-A, non-B hepatitis in recipients. Among donors with higher levels of ALT, that percentage increased further. The results appear in Table 23.1.

A similar relationship was observed in an analysis of data about patients who had received only a single unit in transfusion (Table 23.2). Thirty-three per cent of patients who received a single unit of blood from a donor whose ALT level was between 45 and 59 IUs developed non-A, non-B hepatitis.

From their results the investigators calculated that 40 per cent of the post-transfusion non-A, non-B hepatitis cases would have been prevented if units received from donors who had an ALT level of 45 IUs or greater had been discarded. Discarding those donations would have resulted in a loss of 3 per cent of donations. A higher proportion of cases could have been prevented by discarding units from donors with ALT levels of 30 IUs or greater, but 9 per cent of donations would have been lost.

Table 23.1

TTV study: Frequency of association between donors and recipients with non-A, non-B hepatitis according to donor ALT level

ALT level of donor (IU)	Number of donors in range	Donors associated with (post-transfusion) NANB hepatitis in recipients	
		Number	%
1–14	3,680	329	9
15–29	1,397	179	13
30–44	315	59	19
45–59	85	30	35
60–284	87	41	47

Source: R.D. Ach et al., "Serum Alanine Amino Transferase of Donors in Relation to the Risk of Non-A, Non-B Hepatitis in Recipients," *New England Journal of Medicine* 304, no.17 (April 1981):989–94.

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Table 23.2

TTV study: Relation between ALT level of donor and incidence of non-A, non-B post-transfusion hepatitis among 275 recipients of single units

ALT level of donor (IU)	Number of recipients	Recipients with NANB hepatitis	
		Number	%
1–14	167	7	4
15–29	72	5	7
30–44	24	2	8
45–59	6	2	33
60–284	6	3	50

Source: R.D. Ach et al., "Serum Alanine Amino Transferase of Donors in Relation to the Risk of Non-A, Non-B Hepatitis in Recipients," *New England Journal of Medicine* 304, no. 17 (April 1981):989–94.

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The investigators said that the benefits of implementing ALT screening would have to be weighed against the number of potential donors who would be excluded, the incidence of hepatitis in recipients, and the severity of the disease. On the subject of the severity of disease, they said:

Although non-A, non-B post-transfusion hepatitis is most often subclinical, approximately 20 to 40 per cent of patients who contract this disease are symptomatic. At least 25 percent of all affected patients have aminotransaminase elevations lasting longer than six months. Moreover, a chronic non-A, non-B carrier state that is often asymptomatic has been documented ... The development of chronic hepatitis and progression to cirrhosis have been observed, although the precise frequency of these complications is uncertain.

The investigators acknowledged that there were difficulties in determining what information should be given to donors who were to be excluded, and that there were differences in what was a "normal" ALT level in different donor populations. However, they came to the following conclusion:

Although ALT screening lacks the sensitivity to detect all infectious units and lacks the specificity to detect only infectious units, the high correlation between an elevated ALT level and infectivity of transfused blood provides a compelling argument that such screening should be instituted.

The National Institutes of Health (NIH) study

The results of a similar study by Dr Harvey Alter and colleagues at the National Institutes of Health (the NIH study) were published in August 1981 in the *Journal of the American Medical Association*. The data from this study demonstrated a relationship between donor ALT levels and the development of post-transfusion hepatitis similar to that shown by the TTV study. Based on their data, the NIH investigators calculated that screening donations for elevated ALT levels could prevent 29 per cent of post-transfusion non-A, non-B hepatitis at a loss of 1.6 per cent of donations.

Although similar in design, the NIH study was considerably smaller than the TTV study, involving only 283 open-heart surgery patients who had received blood from 3,359 volunteer donors. All the recipients in the NIH study received more than one unit of blood. The investigators found that 12.7 per cent of recipients developed hepatitis, 97 per cent of which was classified as non-A, non-B. As in the TTV study, the higher the ALT level of the donation, the greater was the risk of acquiring post-transfusion non-A, non-B hepatitis. In this study, 28.8 per cent of recipients of at least one donation with an ALT level of 54 IUs or greater developed hepatitis. Its findings, showing the relationship between the donor's ALT level and the incidence of post-transfusion hepatitis in recipients, appear in Table 23.3. Of the thirty-six hepatitis cases, thirty-five were classified as non-A, non-B.

Table 23.3
NIH study: Relationship of donor ALT level and
transfusion volume to recipient hepatitis

Maximum ALT level of donors (IUs)	No. of recipients	Average no. of units transfused	Recipient hepatitis		
			No.	%	No. of cases per 1,000 units
<33	162	11.2	14	8.6	7.7
34-53	69	12.9	7	10.1	7.9
>54	52	14	15	28.8	20.7

Source: H.J. Alter et al., "Donor Transaminase and Recipient Hepatitis," *Journal of the American Medical Association* 246, no. 6 (August 1981):630-34.

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The investigators did not recommend ALT testing. They described the concerns revealed by the two studies as follows:

The ALT testing of donors is thus a tenuous balance between risk and benefit. The balance shifts toward testing when one considers that approximately 30 per cent of PTH [post-transfusion hepatitis] might be prevented (90,000 cases per year in the United States), but this is tempered by the realization that 70 per cent will not be prevented and that the prevention of 30 per cent is in some doubt unless confirmed by a randomized clinical trial. The balance also shifts away from testing when one considers the estimated additional \$20 million in the annual cost of blood in the United States alone and the potential national loss of 45,000 donors and more than 90,000 blood units. It is a difficult equation, whose solution will require thought and planning.

U.S. debate over ALT testing

The publication of the two studies stimulated a debate in the United States over the value of ALT testing as a surrogate for non-A, non-B hepatitis in the screening of blood donations. The debate was most intense between 1981 and 1983, and appeared in articles, letters, and editorials in the major medical and scientific journals.

An editorial in the *New England Journal of Medicine*, for example, noted that the ALT test lacked sensitivity and as a result would not identify all units of blood capable of transmitting non-A, non-B hepatitis. The authors analysed the consequences, using more complete data than that shown in Tables 23.1 and 23.2. They found that, in the TTV study, 63 per cent of patients who had

received blood with an ALT level greater than 100 IUs did not develop hepatitis and that, if 100 IUs was used as the level above which donations would be rejected for transfusion, 65 per cent of excluded donors would be excluded unnecessarily. Their assessment of the TTV study data suggested that the predicted efficacy of excluding units with ALT levels greater than 100 IUs would be only 21 per cent among patients receiving single units by transfusion. They acknowledged that "screening blood donors with the ALT test appeared to be a promising way to decrease the risk of post-transfusion hepatitis," but concluded that a number of questions required answers before it could be recommended. These questions included how to make the tests uniform from one centre to another, at what ALT level a prospective donor should be excluded, and what excluded donors should be told. The authors also mentioned the increased costs associated with the test kits and the increased recruitment that would be needed to replace the excluded donors.

ALT testing was considered as a surrogate for non-A, non-B hepatitis by several committees in the United States. The first, the ad hoc advisory committee on ALT testing, was established by the National Heart, Lung, and Blood Institute. It consisted of hepatitis experts and representatives of the major blood-banking organizations and of several government agencies. At its first meeting, on 8 January 1981, there was considerable support for the implementation of ALT testing of donors. The members agreed that the TTV study demonstrated that patients had an increased risk of developing post-transfusion non-A, non-B hepatitis if they received blood from donors with elevated levels of ALT, and that blood-banking organizations should prepare to test all the units they collected and to exclude those with elevated levels of ALT. They also recognized that additional work was needed to define the level above which units should be excluded, to standardize test procedures, and to develop guidelines for the notification and deferral of donors with elevated ALT levels. Suggested guidelines were to be published as soon as possible.

The committee's initial support for ALT testing waned during the five and a half months between its first meeting and its next, held on 18 June 1981. At the second meeting, the committee concluded that "the available data [were] insufficient for a decision," and identified the kinds of information needed before a final decision could be made. It wanted information about regional variations in the ALT levels of donors, the causes of ALT elevations, the technical aspects and legal implications of ALT testing, the number of donors who would be excluded, the information to be given to excluded donors, the process of donor deferral, and an analysis of the costs and benefits of ALT testing.

A study carried out by the American Red Cross found that ALT levels in donors varied widely depending on geographic region, sex, alcohol use, and even blood type. It concluded that ALT testing "raises more questions

than it answers." A committee established by the American Association of Blood Banks also rejected the implementation of ALT testing. Its conclusion was published in 1983:

While we share the desire of the entire medical community to reduce the incidence of transfusion associated hepatitis, we believe that currently available evidence does not justify either universal testing of donor blood for ALT or the rejection of donors who have elevated levels. Therefore, at this time we do not advise routine donor testing for ALT as a means of reducing the incidence of non-A, non-B hepatitis.

In March 1983, the issue was considered by the blood products advisory committee of the U.S. Food and Drug Administration. The minutes of this meeting do not record a formal decision, and although no recommendation about ALT testing was made it is apparent that the weight of opinion was against the implementation of ALT as a surrogate test for non-A, non-B hepatitis. By this time, AIDS had emerged as a major threat to the blood supply and was the main focus of the committee's discussions.

According to both Dr James Mosley, a U.S. hepatitis expert and co-investigator of the TTV study, and Dr Thomas Zuck, a blood banker and former senior official of the U.S. Food and Drug Administration, both of whom testified at the hearings, the main reason that the U.S. blood-banking industry did not introduce ALT testing in the early 1980s was that it did not recognize that non-A, non-B hepatitis could produce serious clinical disease in large numbers of persons. Dr Zuck said that the reason ALT testing was not instituted was not because the data from the TTV study were wrong; "it [was] because we really didn't believe it was a serious disease." This was a commonly held view in the early 1980s. Dr Harvey Alter, the principal investigator in the NIH study, wrote in 1980, for example, that "[a]lthough recognition of non-A, non-B hepatitis has been a relatively recent event, a characteristic, though not pathognomonic [indicative of a disease], clinical pattern is beginning to emerge." An editorial in the 11 July 1981 issue of *The Lancet* said:

Although regular users of blood products do get chronic liver disease which is probably due to non-A, non-B agents, there is not much information about the long-term consequences of subclinical hepatitis after a single transfusion episode. In the U.K. there is no report about long-term follow-up of transaminitis patients.

Despite the controversy about ALT testing, some blood centres decided to implement the test routinely. The New York Blood Center, a participant in the TTV study, began routine ALT testing of all donations in 1982. An explanation

for that decision, given by Dr Johanna Pindyck, the director of the Greater New York Blood Program, appeared in the *Journal of the American Medical Association*:

She noted that the New York Blood Center, which takes in some 700,000 units of blood per year, has six donation sites with instrumentation that all must be correlated. "We know we're going to incur extra cost in running the program," she explained, "but we think the cost-benefit ratio is satisfactory." She estimated that ALT testing will add about \$2.40 to the cost of a unit of blood.

Pindyck also defended the test itself ... "The test as a test is just fine," she said. "The technologies are extremely good. It's just that it is not an absolute indicator for NANB hepatitis. But it's the only thing we have to identify donors who are at high risk of transmitting this type of hepatitis."

Pindyck said it probably will be five or ten years before a specific test can be developed for NANB hepatitis and added, "In the meantime, we think we can protect 7,000 to 10,000 people a year in the New York area and, over a five-year period, that adds up to a significant number of people, particularly if you consider that many of those who contract NANB hepatitis will go on to have chronic liver disease."

A handful of other U.S. centres also implemented ALT testing.

Both the TTV and NIH studies were prospective studies; they studied the recipients both before and for several months after transfusion. They were not interventionist studies, in that they did not separate the patients into two groups – one to receive blood that had been tested and found to have normal ALT levels, the other to receive untested blood. Because the TTV and NIH studies did not involve the rejection of any blood donations, they did not demonstrate what actually happened when donations with ALT levels above a certain level were removed. The investigators only estimated, based on careful observation and calculation, what would have happened if such blood donations had been removed. The studies were therefore said to have only predicted, not proved, the efficacy of ALT testing.

The purely predictive nature of the TTV and NIH studies was one of the main reasons given for not implementing ALT testing at most blood centres. That reason was presented, for example, by the committee established by the American Association of Blood Banks to evaluate the efficacy of ALT as a surrogate test when it reported in 1983. In its report, published in the journal *Transfusion*, it said:

No study has shown that the actual elimination of donors with elevated levels of ALT will reduce the incidence of elevated levels of ALT post-transfusion, much less hepatitis. Current studies correlate donor levels

of ALT with posttransfusion levels in the recipient. It is essential to show that elimination of donors with high levels of ALT will, as postulated, reduce the number of recipients who also have high levels. Such studies must be done before drastic changes in donor qualifications can be justified. A decision to test all donors will preclude these essential studies.

This position was supported by Dr Alter and Dr Paul Holland, two of the investigators in the NIH study.

An interventionist study presented problems of medical ethics, however. Two large, well-conducted prospective studies had shown a clear association between elevated levels of ALT in donors and the development of non-A, non-B hepatitis in recipients of transfusions. A further, interventionist study would involve giving some patients blood components known to have elevated ALT levels and other patients components that had been screened for elevated ALT levels. Some blood bankers and researchers felt that the association between elevated ALT levels and non-A, non-B hepatitis had been shown to be so close that an interventionist study would necessarily mean giving some patients safer blood than would be given to others. The ethical problem was acknowledged by Dr Alter, who was reported in the *Journal of the American Medical Association* in December 1981 to have said that a "controlled study would really be the only way to settle this, but that brings up the ethical and moral questions, and I doubt that a controlled study ever will be done." Moreover, as Dr Mosley testified, if ALT testing of donors were ever implemented on a national basis – effectively establishing a national standard – it would be ethically impossible to conduct such a study.

No such study was ever conducted in the United States. In addition to the ethical issue, there was concern about the time that would be required and the cost. Dr Mosley, who was involved in the TTV study, said that that study had cost \$7.5 million dollars over six years. He estimated that an interventionist study conducted in the early 1980s would have required four years and even more money.

Consideration of ALT testing in Canada

Although the use of ALT as a surrogate test for non-A, non-B hepatitis had been discussed in the United States as early as 1975, the possibility was not considered in Canada until 1981, the year the final results of the TTV and NIH studies were published. The delay in consideration was not because blood bankers and researchers in Canada were unaware of the studies being conducted in the United States. The preliminary results of the TTV and NIH studies were known in this country as early as 1978.

Dr John Derrick, the director of operational research of the Canadian Red Cross Society (Red Cross), was monitoring developments in the United States, including the meetings that took place in the early 1980s. The first recorded

discussion of the issue by the Red Cross was at a meeting on 24 April 1981 of the blood transfusion service advisory committee. Although the final results of the TTV study on ALT had not yet been published, Dr Derrick reported that

there was a definite feeling in the United States that introduction of ALT testing would take place within the next year or so. A group of people was to meet in June, in Washington, D.C., at which the B.T.S. [blood transfusion service] would be represented, to discuss the matter further ... In the meantime, we are keeping the matter under review, and are maintaining a close liaison with the American Red Cross Blood Programme.

On 13 July 1981, Dr Derrick and Dr Roger Perrault, the national director of the blood transfusion service, attended a meeting at the Bureau of Biologics, the federal body responsible for the regulation of blood products. There, according to the minutes of the meeting, they reported the steps the Red Cross had taken in response to the "surge of interest" in the ALT test. Dr Perrault told the meeting that the blood transfusion service advisory committee had recommended further study of the evidence and implications for testing, with further consideration to be given at a meeting in the autumn.

ALT testing was again discussed by the blood transfusion service advisory committee at a meeting on 13 November 1981 attended by Dr Alastair Clayton, the director general of the Laboratory Centre for Disease Control. Dr Clayton estimated that the use of ALT testing might prevent four or five cases of post-transfusion hepatitis per year. He did not feel that the expense of ALT testing could be justified.

There were no reliable data that would have supported Dr Clayton's estimate that only four or five extra cases of post-transfusion hepatitis would be prevented. Even if one assumed that ALT testing would reduce the incidence of post-transfusion non-A, non-B hepatitis by only 20 per cent (the TTV and NIH studies had predicted closer to 30 per cent), his estimate would imply that there were only twenty to twenty-five cases of post-transfusion hepatitis in Canada per year. Dr Perrault, Dr Martin Davey, the assistant national director of the Red Cross's blood transfusion services, and Dr Victor Feinman, a leading Canadian hepatologist, agreed in testimony that the actual number of cases would have been considerably higher. Dr Davey said that he would have expected even the number of reported cases to be higher.

At that time, non-A, non-B hepatitis was not yet isolated in the national statistics for notifiable diseases. In the absence of national statistics and of any studies on the incidence of post-transfusion non-A, non-B hepatitis in Canada, the only possible basis for an estimate of incidence was a comparison with the United States. In the early 1970s, the proportion of blood donors who tested positive for hepatitis B at the Red Cross blood centre in Toronto was

slightly higher than that of volunteer donors studied at the National Institutes of Health during the same period. Although most centres in Canada had a lower rate, Montreal's was significantly higher. Dr Mosley testified that, given the similarity in the prevalence of hepatitis B among Canadian and U.S. blood donors, in the absence of evidence to the contrary one could prudently assume that the incidence of post-transfusion non-A, non-B hepatitis would also be similar.

In his testimony, Dr Davey agreed that, in the absence of specific data, this was a reasonable hypothesis, but he said he believed at the time that the severity of the problem in Canada needed study. This is the position he took at a meeting of the blood transfusion service advisory committee meeting on 13 November 1981, when he said there were "no adequate data in Canada and no action should be taken until Canadian data indicated that such steps were necessary." Dr Davey's position was endorsed by the committee, which decided that the hepatitis working group "should continue to hold a watching brief on this subject and that no action should be taken at the present time." Dr Davey testified that he had hoped that the working group would develop a proposal to study the incidence of post-transfusion non-A, non-B hepatitis in Canada.

The hepatitis working group had been established during the 1970s, when hepatitis was the primary infectious complication associated with blood transfusion. Its membership was drawn from the blood transfusion service and consisted of representatives of the national office, the national reference laboratory, and the medical directors of some of the seventeen blood centres. The working group considered a wide variety of issues related to hepatitis and post-transfusion hepatitis, including donor screening, the evaluation of different hepatitis tests, the policies and procedures for the collection of plasma, procedures to follow individual cases of post-transfusion hepatitis, and measures to identify and defer donors implicated in cases of post-transfusion hepatitis. It also considered other issues, such as testing for cytomegalovirus. During the 1980s, its concerns became increasingly technical in nature, and it evolved into the immunology and virology working group. Although both issues were appropriate for it to consider, the hepatitis working group never considered a study of the incidence of post-transfusion hepatitis in Canada or the desirability of surrogate testing for non-A, non-B hepatitis. Moreover, there is no evidence that the hepatitis working group monitored the issue of ALT testing as a surrogate test for non-A, non-B hepatitis, as the blood transfusion service advisory committee had decided it should in November 1981.

Anti-HBc as a surrogate test

The presence of antibody to the hepatitis B core antigen (anti-HBc) is a specific indication of earlier hepatitis B infection, and is also used as a surrogate marker both for infection with HIV and for non-A, non-B hepatitis. The ALT

test described previously measures a marker of liver damage, which is associated with hepatitis. Anti-HBc tests, in contrast, identify the presence of an antibody that indicates previous exposure to the hepatitis B virus, which is epidemiologically similar to the viruses that cause AIDS and non-A, non-B hepatitis. The use of anti-HBc as a surrogate test is based on the proposition that, because the risk factors for acquiring blood-borne infections are similar (for example, through injection of drugs), a blood donor exposed to one blood-borne virus (hepatitis B) is more than normally likely also to have been exposed to others, including those that cause AIDS and non-A, non-B hepatitis.

Anti-HBc testing had been suggested as a surrogate test for non-A, non-B hepatitis in the early 1980s, but research into its efficacy lagged behind that for ALT. Then, from 1983 to 1985, as AIDS became the focus of concern, interest in surrogate testing for non-A, non-B hepatitis declined generally. The consideration of surrogate testing in the United States during those years was directed mainly towards AIDS. Both ALT and anti-HBc were proposed as surrogate tests for AIDS but, because AIDS afflicted principally the same groups as were at high risk of contracting hepatitis B – namely, homosexuals, intravenous drug users, and hemophiliacs – anti-HBc was given more serious consideration. In December 1983, the U.S. Food and Drug Administration's blood products advisory committee decided to establish a special group to study the use of anti-HBc as a surrogate test for AIDS. The group did not reach a consensus, and the majority of members were opposed to the implementation of anti-HBc testing for this purpose. By the time the group reported in July 1984, however, HIV had already been identified. When testing for HIV antibody became possible, interest returned to the use of anti-HBc as a surrogate test for non-A, non-B hepatitis.

The TTV study, which examined the efficacy of both ALT and anti-HBc as surrogate tests for non-A, non-B hepatitis, published its preliminary findings with respect to anti-HBc in September and October 1981. They indicated that the incidence of non-A, non-B hepatitis among recipients of anti-HBc-positive blood was three times greater than it was among those who received anti-HBc-negative blood. A major Australian study, published in January 1982 in *The Lancet*, supported these preliminary findings. It found that, of an incidence of post-transfusion hepatitis of 2 per cent, 78 per cent was non-A, non-B. It also found that the patients in the study who developed non-A, non-B hepatitis had received "a significantly higher proportion" of units of blood containing anti-HBc than had the other patients in the study. The Australian investigators concluded that anti-HBc screening of blood donations might reduce the number of cases of post-transfusion non-A, non-B hepatitis by half. Although the debate was less intense than it was about ALT testing, these studies prompted discussion about anti-HBc as a surrogate test for non-A, non-B hepatitis.

The transfusion transmitted viruses (TTV) study

The final results of the TTV study relating to anti-HBc were published in December 1984 in the *Annals of Internal Medicine*. They confirmed the preliminary data. Of the 1,151 recipients examined, 9.2 per cent developed non-A, non-B hepatitis. The incidence of non-A, non-B hepatitis was 2.6 times greater among recipients of at least one unit of anti-HBc-positive blood than it was among recipients of blood that was anti-HBc negative. This relationship is shown in Table 23.4. More than one-third of the recipients who developed non-A, non-B hepatitis had received at least one unit of anti-HBc-positive blood.

The investigators also analysed the anti-HBc and ALT data together. Of patients who developed non-A, non-B hepatitis, 34.9 percent received anti-HBc-positive units; and 36.8 per cent received blood with an ALT level equal to or greater than 45 IUs. The ALT and anti-HBc tests identified different subsets of donors, however. Only 8.6 per cent of anti-HBc-positive donors had ALT levels equal to or greater than 45 IUs. The investigators asked, as a result, whether, in the interest of safety, both tests should be used. The combined efficacy of the two tests was estimated to be 53.8 per cent, or 61.2 per cent when adjusted to take into account the fact that some of the patients in the study were at risk of acquiring hepatitis from other sources. Screening for anti-HBc would result in the discarding of 5.1 per cent of units donated, as compared with only 2.8 per cent if donations with ALT levels of 45 IUs or greater were excluded. Because the tests identified different populations, 7.5 per cent of units would be discarded if both tests were used. These data are summarized in Table 23.5.

Table 23.4

TTV study: Incidence of non-A, non-B hepatitis in recipients as related to hepatitis B core antibody status of their donors

Donor anti-HBc status	Number of recipients	Recipients with NANB hepatitis	
		Number	%
All negative	953	69	7.2
Any positive	198	37	18.7

Source: C.E. Stevens et al., "Hepatitis B Virus Antibody in Blood Donors and the Occurrence of Non-A, Non-B Hepatitis in Transfusion Recipients," *Annals of Internal Medicine* 101, no. 6 (December 1984):733.

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Table 23.5

TTV study: Effect of donor screening for hepatitis B core antibody (anti-HBc) or alanine amino transferase (ALT) on the expected incidence of non-A, non-B hepatitis (per cent)

	Efficacy rate when donors excluded by screening for		
	anti-HBc	ALT \geq 45 IU/L	Both
Crude efficacy	34.9	36.8	53.8
Corrected efficacy	21.4	29.9	39.2
Adjusted for control rates, when corrected	33.3	47.4	61.2
Units discarded	5.1	2.8	7.5

Source: C.E. Stevens et al., "Hepatitis B Virus Antibody in Blood Donors and the Occurrence of Non-A, Non-B Hepatitis in Transfusion Recipients," *Annals of Internal Medicine* 101, no. 6 (December 1984):733.

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The investigators concluded that, until a specific test for non-A, non-B hepatitis was developed, "the use of nonspecific tests to screen donors might be considered as a means of preventing at least some post-transfusion non-A, non-B hepatitis." Rather than suggesting the use of both tests, however, they recommended ALT testing alone:

The data presented indicate that anti-HBc screening of donors might prevent about one third of the cases of non-A, non-B hepatitis attributable to transfusion compared with nearly one half for ALT screening. Moreover, an important disadvantage of anti-HBc screening is that more units of blood would be discarded than if ALT screening were used. For these reasons, the consensus of the study group is that ALT screening of donors is favoured over anti-HBc screening.

The findings were the subject of an editorial in December 1984 in the *Annals of Internal Medicine* by Dr Alter and Dr Holland, who were investigators in the NIH study. They called the TTV study "a superbly conducted, controlled, prospective study," and added that the "criteria for assessing hepatitis were valid and patient follow-up was excellent." They described the data as accurate and valid and said that their study at the National Institutes of Health, which was not yet published, had produced similar results. They did not, however, endorse the recommendation that ALT testing be

implemented, and they said that the true efficacy of surrogate testing could be proved only by a randomized trial that compared tested and untested blood, as had been suggested in 1981.

There are three options in regard to anti-HBc and ALT testing. The first is to decide that existing data are inconclusive, and that in view of problems of nonspecificity, diagnostic uncertainty, responsibility to the donor, test standardization, cost, and donor loss, it is best not to adopt routine donor anti-HBc or ALT testing at this time.

The second option would be to decide that, although the data relating to anti-HBc and ALT efficacy are not definitive, they are scientifically valid and, overall, are sufficiently compelling to warrant universal donor testing at this time. Implicit in this is the assumption that if an interpretive error is to be made, it is best to err on the side of recipient safety and that to withhold such testing is ethically unjustified.

The third option is that existing data are inconclusive, but are sufficiently compelling that a definitive answer must be sought. Implicit is the assumption that efficacy based on predictions from a nonrandomized study is not the same as efficacy established by a randomized, controlled trial ... Although it may be construed as unethical to withhold a given interventional measure, history has shown that it may be equally unethical to withhold the proper study ...

It is our opinion that the third option is the most tenable alternative. Had this controlled study been done 3 years ago when first proposed, a definitive answer would be at hand. Instead, the same uncertainties persist. A multicentre, randomized controlled trial could be completed in 1.5 years, address both the ALT and anti-core issues, and provide a definitive and rational basis for making these complex decisions. Even at this late date, such a study should be done, lest 2 years from now we find ourselves still far from the core (or the ALT) of this issue.

By 1986, however, no such study had been undertaken. In that year the final results of the NIH study were published.

The National Institutes of Health (NIH) study

The NIH investigators, like their counterparts in the TTV study, analysed their data on ALT and anti-HBc in two phases. Preliminary data relating to anti-HBc were published in an abstract in 1984; the final results were published in April 1986. The final results indicated that the incidence of post-transfusion non-A, non-B hepatitis was nearly three times greater in recipients of anti-HBc-positive units than in recipients of units that tested anti-HBc negative; 11.9 per cent of recipients of at least one unit of anti-HBc-positive blood developed post-transfusion non-A, non-B hepatitis, compared with 4.2 per cent of recipients of anti-HBc-negative units. The investigators calculated that

43 per cent of cases of non-A, non-B hepatitis could have been prevented if anti-HBc had been used to screen donations. The specificity of the test was poor, however, and 88 per cent of anti-HBc-positive units were not associated with the transmission of hepatitis and would have been excluded unnecessarily. As in the TTV study, testing for anti-HBc and ALT identified two different populations.

The NIH investigators predicted that a randomized study would not be carried out because the "increased time, cost, and complexity of such a study do not appear to be logistically, financially, and perhaps ethically feasible," given current research priorities. They said that, in "the absence of a prospective controlled study, the existing database must be used to decide whether or not to adopt the ALT test, the anti-HBc test, or both." Whereas the TTV study investigators had proposed ALT as a single surrogate test, the NIH investigators, on the basis of their data, recommended anti-HBc as the better indicator. They said that a specific test for non-A, non-B hepatitis was unlikely to be developed in the near future, and that non-A, non-B hepatitis could cause severe clinical disease in a significant proportion of infected persons. They concluded:

If, as predicted, surrogate screening of blood donors could prevent approximately one third of these cases, then this could represent an annual reduction of 50,000 cases of hepatitis and 2500 cases of cirrhosis. The potential to achieve this degree of disease prevention now appears to outweigh the disadvantages inherent in the adoption of surrogate tests for the non-A, non-B virus carrier state.

By the time the study's final results were published in April 1986, the two major blood-banking organizations in the United States, the American Association of Blood Banks and the American Red Cross, had decided that both surrogate tests should be implemented.

Surrogate testing of plasma for blood products

In April 1984, Cutter Laboratories Inc. (Cutter), the U.S. pharmaceutical manufacturer that was under contract to fractionate Canadian plasma, began anti-HBc testing of the plasma it used to manufacture commercial blood products for sale on the open market. The procedure was intended as a surrogate test for AIDS. The Canadian Red Cross Society then became concerned that the U.S. Food and Drug Administration would require all U.S. manufacturers to implement anti-HBc testing. If this occurred, the Red Cross might also have to test for anti-HBc in order to be able to continue to send Canadian plasma to the United States for fractionation. In January 1985, however, Cutter had stopped the practice. Factor concentrates continued to transmit non-A, non-B hepatitis, however, and attention again began to focus on ALT as a surrogate test for non-A, non-B hepatitis.

In the spring of 1985, Germany's regulatory authority required ALT testing, effective 1 July of that year, of all plasma used in the preparation of coagulation factor concentrates. To be acceptable for use in Germany, the concentrates had to be prepared from plasma with ALT levels less than twice the upper limit of normal. To comply with this regulation, U.S. corporations that exported factor concentrates to Germany began to test a portion of their plasma for ALT levels. Plasma that met the German standard was designated for use in factor concentrates to be exported there. Plasma found to have ALT levels of between two and five times the upper limit of normal was included in pools that would be used to manufacture factor concentrates destined for elsewhere. Any units of plasma with ALT levels greater than five times the upper limit of normal were discarded, and their donors were deferred until their ALT levels fell below two times the upper limit of normal. The fractionators thus implicitly acknowledged that there was a greater risk associated with units with elevated ALT levels, but they were testing only a portion of the plasma processed into concentrates.

As a result, the plasma pools from which factor concentrates were produced for use in North America contained a greater percentage of units with elevated ALT levels than those destined for the German market, and were understood therefore to present a higher risk of infection. The U.S. Food and Drug Administration's division of blood and blood products did not believe that routine ALT testing was warranted at the time, but it was uncomfortable with the use of plasma known to have elevated levels of ALT. The issue was considered by the Food and Drug Administration's blood products advisory committee on 24 April 1985, but no solution was proposed and the committee simply resolved that "product safety ... should not be compromised by having batches with differing levels of quality as a result of implementation of ALT testing on products delivered outside the country."

The U.S. National Hemophilia Foundation, concerned about the high rate of transmission of non-A, non-B hepatitis through factor concentrates to hemophiliacs, raised the question of a U.S. ban on the use of plasma with ALT levels above a certain limit, similar to that in Germany. The issue was discussed on 1 November 1985 at a joint meeting of the foundation and the Canadian Hemophilia Society. Arguments were presented both for and against such a regulation. Dr Zuck, who had recently been appointed the director of the division of blood and blood products, said that the Food and Drug Administration did not need to regulate such a standard because all but one manufacturer was by then rejecting plasma with an ALT level greater than twice the upper limit of normal, and that he would discuss the matter with that one corporation.

Dr Derek Naylor, the director of blood products services of the Canadian Red Cross, attended the joint meeting. In preparation for the discussion and in the absence of any recent consideration of ALT testing by his organization,

Dr Naylor requested the guidance of the hepatitis working group in formulating a position. The minutes of its meeting of 29 October 1985 record the following discussion:

The United States accepts plasma that has ALT levels at up to five times the normal level. As Canada imports much plasma from the United States, what should our position be? The Canadian Red Cross B.T.S. [blood transfusion service] will not determine ALT levels in donor bloods. Nevertheless we do not wish to have plasma that remains after the low-level plasma has been sent to West Germany. It was decided that the Red Cross would prefer to have their fractionated products made from plasma unscreened for ALT.

There is no evidence in the minutes that the working group considered either the reasoning behind the German standard or the TTV and NIH studies, which might have supported a similar decision in Canada. At the joint meeting, Dr Naylor said that it was "unlikely that ALT testing will be introduced for the screening of blood donations" by the Canadian Red Cross. The hepatitis working group's recommendation was not reconsidered after the Red Cross became aware that the U.S. fractionators had begun to test for ALT levels. The Red Cross made this decision without consulting the Canadian Hemophilia Society, its medical and scientific advisory committee, or the Bureau of Biologics. There was no formal discussion by the Canadian Hemophilia Society about the decision until 1987.

Surrogate testing of donated blood in the United States

Consideration of surrogate testing of blood donations to be used for transfusion began again in the United States at about the same time as consideration of ALT testing of plasma to be used for fractionation. By this time, data on the serious clinical consequences of non-A, non-B hepatitis had become clearer. At an international symposium on viral hepatitis held in San Francisco on 8–10 March 1984, Dr Alter of the National Institutes of Health presented new data that showed that as many as 20 per cent of persons with chronic hepatitis develop cirrhosis. Dr Alter presented similar data at an American Red Cross symposium conducted in May 1984, which was attended by two representatives of the Canadian Red Cross.

In October 1985, Dr Joseph Bove, the chair of the American Association of Blood Banks' transfusion transmitted diseases committee, lent his support to anti-HBc testing and said that its swift implementation would both "improve ... public relations and enhance the safety of the blood supply." The issue was considered by the committee he chaired at a meeting on 25 November 1985, at which Dr Alter presented the NIH data on the efficacy of ALT and anti-HBc testing. Although anti-HBc testing would result in more units being discarded, the committee recommended the use of anti-HBc rather than ALT

because it produced a consistent result and was easier to explain to donors. In its recommendation, the committee referred to the high incidence of post-transfusion non-A, non-B hepatitis (between 7 and 17 per cent) and the growing recognition of its serious long-term consequences. The association's board of directors considered the committee's recommendation during a meeting held on 24–25 January 1986, but did not adopt it. The board deferred making a decision about surrogate testing until its next meeting, and agreed to continue to gather information.

The issue was also discussed by the medical directors of the American Red Cross on 16 December 1985. Dr Alter again presented the NIH data. According to a report in the Council of Community Blood Centers newsletter, "most members felt that anti-HBc testing of donors offer[ed] a reasonable promise of improving the safety of blood transfusion and should be further evaluated." The medical directors decided to postpone a decision, however, until they had the results of a one-week pilot study in which anti-HBc testing would be performed at many American Red Cross centres throughout the United States to determine the number of donors who would be deferred. Interim results from this study were available in February 1986 and indicated that on average 2.5 per cent of donors (with a range of 0.6 to 4 per cent, depending on region) would test positive for anti-HBc and would have to be deferred.

The blood products advisory committee of the U.S. Food and Drug Administration considered surrogate testing of blood for non-A, non-B hepatitis at a meeting on 13–14 February 1986. Dr Alter attended and, in addition to presenting data from the NIH study, predicted that 5 per cent of patients who received transfusions would develop hepatitis and 10 per cent of those would develop cirrhosis. He estimated that anti-HBc might prevent one-third of these cases and recommended that it be adopted. Dr William Sherwood reported the results of a study, conducted at the Pennsylvania–New Jersey Red Cross, that indicated that ALT testing would prevent 48 per cent of post-transfusion non-A, non-B hepatitis cases, anti-HBc testing would prevent 45 per cent, and the two tests together would prevent 65 per cent. Dr Girish Vyas, of the University of California at San Francisco, described the experience of the Irwin Memorial Blood Bank in implementing anti-HBc testing, which indicated that 35 per cent of post-transfusion hepatitis cases could be prevented by anti-HBc testing. Dr Peter Levine of the National Hemophilia Foundation emphasized that hepatitis was a serious illness among hemophiliacs, and reported that one study had found that 15 per cent of hemophiliac patients developed cirrhosis.

The blood products advisory committee decided that both ALT and anti-HBc testing should be implemented. After the decision was made, however, some members argued that it would be unwise to remove anti-HBc-positive units from plasma pools that were to be used to produce immune globulins.

The recommendation was therefore amended to restrict surrogate testing to donations of whole blood. Although the committee was concerned only about testing for anti-HBc, it did not then discuss testing the ALT level of plasma that was to be used for fractionation. A year later, when it met on 12–13 February 1987, the committee recommended that plasma from plasma-pheresis be tested for ALT but not for anti-HBc.

The voluntary blood organizations in the United States were quick to respond to the recommendation of the Food and Drug Administration's advisory committee. On 26 March 1986 the American Association of Blood Banks and the American Red Cross announced that, "in consideration of new information," they recommended that blood collection agencies "begin planning to implement additional testing of donor blood which may reduce the risk of non-A, non-B post transfusion hepatitis." In April, the board of directors of the American Association of Blood Banks decided that both ALT and anti-HBc testing should be implemented, and that both should become requirements of the association's standards accreditation program and thus, in effect, a national standard. The target date for the implementation of both tests by the association's members (the great majority of voluntary community and hospital blood banks in the United States) was 1 August 1986, but it was later extended to 30 November. The date for anti-HBc testing was extended until after a workshop organized by the Food and Drug Administration in January 1987, which was scheduled to "review the status of surrogate testing" and to "establish policies, regulations, and standards." The issues discussed at that workshop included the number of donors excluded on the basis of elevated ALT levels and positive anti-HBc tests, the ALT levels above which donors should be excluded, regional differences in the ALT levels of donors, and the sensitivity of the anti-HBc test.

Despite the recommendation of its own blood products advisory committee and the implementation of surrogate testing by the country's major blood-banking organizations, the Food and Drug Administration did not issue a regulation requiring anti-HBc testing of donated blood until March 1991, and then it was for the purpose of identifying units contaminated with hepatitis B. It never issued a regulation requiring testing for ALT levels. The lack of regulation was consistent with the administration's approach that regulation was unnecessary if there was voluntary compliance. This was the approach it had also taken with regard to ALT testing of plasma for fractionation and testing for HIV antibody. Another reason for the absence of regulation was the difficulty the administration encountered in licensing anti-HBc tests intended for screening blood donations. The criteria for licensing test kits for screening blood donors were well-suited for kits that tested for a specific marker, but they had not been designed for non-specific or surrogate tests.

Canada's Rejection of Surrogate Testing

There was considerably less discussion about post-transfusion hepatitis in Canada than in the United States in the early 1980s. Only one study was conducted in Canada into the efficacy of ALT testing before 1988. It was a small study conducted in Montreal between August and October 1981, which also examined the incidence of post-transfusion hepatitis. The results, published in the journal *Clinical and Investigative Medicine* in 1983, showed an 8 per cent incidence of post-transfusion hepatitis. Blood donations with high ALT levels were not associated with post-transfusion hepatitis more frequently than those with normal ALT levels. The data were taken from only twenty-four recipients of transfusions, however, and because of the small sample the investigators decided that the results could not be "considered conclusive."

The lack of attention to hepatitis-related issues was a source of frustration for Dr Brian Moore, the director of the Canadian Red Cross Society (Red Cross) national reference laboratory, who had studied hepatitis issues for many years. Dr Moore attended a meeting of the International Society of Blood Transfusion in Munich in July 1984, shortly after the discovery of the causative agent of AIDS, when a specific test for AIDS was expected to be available soon. Dr Moore's view on his return was that "the introduction of a specific test for AIDS must not be allowed to divert us in our role as transfusionists from our principal aim, which is the elimination of 'non-A, non-B' hepatitis." Dr Moore recommended to Dr Roger Perrault, the national director of the blood transfusion service, that the Red Cross implement anti-HBc testing (described in the previous chapter) as an interim measure to screen for non-A, non-B hepatitis. Dr Perrault did not agree. He said that

[w]hat I do agree with ... is that a meeting of experts on hepatitis should be convened with a view to clarifying the best possible role that our National Transfusion Service can play in reducing the incidence ... of transfusion-associated hepatitis (with particular attention to non-A, non-B).

There were then almost no data on the extent of post-transfusion non-A, non-B hepatitis in Canada. The need for more information was raised by Dr Gail Rock, the medical director of the Ottawa blood centre, at a meeting on 27 March 1984 with several persons from the Red Cross's national office, including Dr Perrault and Dr Martin Davey, the assistant national director of the blood transfusion service. At that meeting, it was agreed that a multicentre study was needed to determine the incidence of post-transfusion non-A, non-B hepatitis in Canada and that the most suitable blood centres to participate were those in Toronto, Montreal, Ottawa, Edmonton, and Vancouver.

In fact, a study of the incidence of post-transfusion hepatitis had already been started by Dr Victor Feinman at the liver study unit of Mount Sinai Hospital in Toronto approximately three months earlier. When a separate Red Cross study was proposed during a meeting of Red Cross medical directors, held on 29–30 March, the acting medical director of the Toronto blood centre told his colleagues about Dr Feinman's study. It was decided that Dr Feinman's research plan should be reviewed, after which it could be determined whether a Red Cross study was still required.

Unlike the TTV and NIH studies in the United States, Dr Feinman's study (the Toronto incidence study) was not designed to examine the efficacy of surrogate tests. It was designed only to determine the incidence of non-A, non-B hepatitis in patients who had received transfusions. Recipients were tested for ALT levels before and after transfusion solely to identify cases of post-transfusion non-A, non-B hepatitis. The blood components transfused were like all others distributed to the local Red Cross blood centre and had not been subject to any special form of screening or surrogate test for ALT levels or the presence of anti-HBc. As a result, the Toronto incidence study was not able to produce data on the efficacy of surrogate testing. Arrangements had been made, however, for the Toronto blood centre to retain samples of donors' blood so that, when a case of transfusion-associated hepatitis was identified, the research laboratory at Mount Sinai Hospital could further analyse that sample. In addition, the Toronto blood centre had agreed to encourage implicated donors to contact the liver study unit of Mount Sinai Hospital for laboratory tests and clinical assessment.

The Red Cross knew of the limitations of the Toronto incidence study. The design of the study, including possible modifications to it, were discussed by Dr Feinman and Red Cross staff members shortly after the medical directors met. Dr Feinman was prepared to expand the focus of the study to examine the association between ALT levels in donors and the development of post-transfusion hepatitis in recipients. He wrote to Dr Perrault that

the study gives the Red Cross a golden opportunity to obtain information regarding potential infectivity of donors whose sera have elevated ALT. This aspect is not a major part of our project, but it will supply very important information for the Red Cross and ourselves.

The study was never modified to secure this information, however. Dr Davey testified that the Red Cross had no way of knowing which blood donations would be sent to Mount Sinai Hospital; as a result, short of testing all donations at the Toronto centre, it had no way of determining the ALT levels of the units involved in the study. The stored samples from implicated units could not be tested after they reached Mount Sinai Hospital because ALT tests were unreliable unless they were carried out soon after the blood was donated.

Despite the limitations of the Toronto incidence study, and the fact that it was being conducted in only one centre, the Red Cross decided not to conduct a multicentre study on its own. Instead, the Red Cross agreed to continue giving Dr Feinman stored samples of any donations subsequently implicated in cases of post-transfusion hepatitis. Dr Davey testified that these samples were not stored specifically for the Toronto incidence study, but were kept routinely for several months. Ultimately the Red Cross stopped sending Dr Feinman the samples it had in storage because they were needed for AIDS research.

The incidence of post-transfusion hepatitis and the efficacy of surrogate testing were discussed by representatives of the Red Cross and the Canadian Liver Foundation in the summer of 1984. The foundation, a not-for-profit organization concerned with preventing liver disease, was thinking about organizing a symposium on viral hepatitis that would be a first step towards establishing a continuing scientific body to examine hepatitis-related issues. Dr James Rankin, the director of the foundation's epidemiology unit, described the discussion in a letter he wrote soon after the meeting. According to Dr Rankin, Dr Perrault said that "there was little to be gained in holding a symposium in which the major contributors came from outside of Canada and told Canadians what they already know" and suggested instead that a small working party be formed to assess "the nature, magnitude and consequences of infection with non-A, non-B hepatitis in Canada." The possibility of collaborating on studies of the incidence and prevention of viral hepatitis was also considered, including the possibility that the Toronto incidence study might serve as "a pilot for a larger project in Canada." In September 1984, Dr Davey wrote to Dr Rankin that the Red Cross had among its priorities the need to "obtain accurate information about the incidence of transfusion-associated hepatitis in Canada" and to "reduce the transmission of viral hepatitis by Canadian blood donors, in particular, the application of more sensitive screening tests." A multicentre study of the incidence of post-transfusion hepatitis and the efficacy of surrogate testing in Canada was not proposed, however, until 1987.

Preliminary results of the Toronto incidence study were made available to Dr Davey and Dr Roslyn Herst, the deputy medical director of the Toronto blood centre, on 24 September 1984. In 271 patients studied for six months, the incidence of post-transfusion hepatitis was 4 per cent. At this time it was still intended that Dr Feinman would be given the stored samples from all implicated donors, and Dr Davey confirmed in a letter to Dr Feinman that

"follow-up sera from blood donors can be obtained when required." By 9 July 1985, 315 patients had been followed for six months or more and the incidence, based on preliminary and incomplete data, had risen to 7.6 per cent. Between 150 and 160 donors were implicated. The stored samples from these donors were given to Dr Feinman, but Dr Davey told him that "future arrangements for access to stored sera may have to change, as these are to be retained longer in case needed for investigation re AIDS." Dr Davey later wrote in a memorandum, with a copy to Dr Perrault, that

[t]his study, while behind its schedule, is meeting its objectives. Lack of a control group remains a drawback. It provides worst case estimates of the incidence of transfusion-associated hepatitis, at ~ [approximately] 8 per cent, and consequent chronic liver disease, at ~1 per cent of patients transfused.

Dr Davey testified that he had no reason at that time to expect the final results to be drastically higher or lower than the preliminary data. He also said that he was concerned when the second set of preliminary data revealed so high an incidence.

Canada's response to developments in the United States

Throughout the 1980s, the Canadian Red Cross had a close relationship with the American Red Cross and followed its discussions of surrogate testing. The national director of the Canadian blood transfusion service, Dr Perrault, attended at least one meeting of the American Red Cross blood services committee at which surrogate testing was discussed. The Canadian Red Cross also knew about potential regulatory developments in the United States and the deliberations of the U.S. Food and Drug Administration's blood products advisory committee, described in the previous chapter. Dr Derrick, who at the time was a special adviser to Dr Perrault, attended the meeting of that committee in February 1986 at which the implementation of both surrogate tests was recommended, and wrote a detailed report of it which he distributed to his colleagues.

The Canadian Red Cross was also aware of developments in the policy of the American Association of Blood Banks regarding surrogate testing through Dr Jacob Nusbacher, who was a member of the association's standards subcommittee in 1984 and 1985 and who had come from the United States to become the medical director of the Toronto blood centre. Dr Nusbacher forwarded the literature about surrogate testing to Dr Perrault, Dr Davey, and Dr Herst in December 1985, with the comment:

if the AABB committee on standards is going to make screening for Non-A, Non-B a standard, the pressure will be on us to do likewise. Perhaps we ought to take a leadership role in this area (especially if we decided testing is desirable).

Personally, I am not certain how I feel about this issue. If I were in Rochester (where I was over collected by 15 per cent), the decision would be easier.

Dr Nusbacher said he would inform Dr Perrault of the result of the subcommittee's deliberations.

On 7 January 1986, Dr Nusbacher told Dr Perrault that the subcommittee would be recommending surrogate testing, and that he had received information that the American Red Cross was "gearing up for testing." In Dr Nusbacher's view the Canadian Red Cross would "have no choice but to implement testing" for anti-HBc if the Americans did so. The same day Dr Perrault wrote to Dr Denise Leclerc-Chevalier, the executive director of the Canadian Blood Committee, the agency through which the provinces funded the Canadian blood program. He said that the principal blood-banking organizations in the United States were thinking of introducing anti-HBc as a surrogate test for non-A, non-B hepatitis. He told her that the publication of the final NIH data was imminent and that it would predict that anti-HBc screening of donors might have prevented 43 per cent of non-A, non-B hepatitis at the loss of 4 per cent of donors. He wrote:

We also plan to look carefully at the results of a study carried out by Dr Victor Feinman at the Mount Sinai Hospital on non-A, non-B hepatitis in blood transfusion recipients, but using another test (ALT). It will be very important to see if there is any difference between Canadian and American data in this regard as the implementation of another screening test will mean a significant expenditure to the Canadian Red Cross Programme.

This statement appeared in the context of a discussion about surrogate testing, and in particular in association with a reference to the NIH study of the efficacy of surrogate testing. A reader might reasonably infer from it that the Toronto incidence study was evaluating ALT testing as a surrogate test for non-A, non-B hepatitis. Dr Feinman was indeed measuring ALT levels, but as a diagnostic tool to identify occurrences of hepatitis in the recipients of transfusions. No ALT testing had been conducted on the blood donations that the patients had received. The Red Cross knew this and had told Dr Feinman it could not isolate for testing the donations sent to Mount Sinai Hospital. The Toronto incidence study was not in fact designed to evaluate the efficacy of ALT as a surrogate test for non-A, non-B hepatitis. During his testimony, Dr Perrault was asked whether he had not understood that the Toronto incidence study could not evaluate the efficacy of ALT as a surrogate test. He first responded that he did not recall having made this distinction; later he disagreed that someone reading his letter would have been left with the impression that the study was investigating ALT as a surrogate test.

Over the next several months similar statements to the one by Dr Perrault quoted above were made in the position papers prepared for meetings of the medical directors of the local blood centres, the advisory committee of the blood transfusion service, and the advisory subcommittee of the Canadian Blood Committee, and during the meetings at which those papers were discussed. All would leave the impression in a reasonable reader or listener that the Toronto incidence study being conducted by Dr Feinman was examining the efficacy of ALT testing as a surrogate test for non-A, non-B hepatitis.

The first of these position papers was prepared as background information about surrogate testing for a meeting of the Red Cross medical directors on 3 March 1986. It explained that surrogate testing was not implemented in Canada but that "a Toronto-based study (Dr V. Feinman) [of] post-transfusion hepatitis did include ALT testing but not anti-HBc" and that the results from that study would be available soon. A document attached to the position paper contained preliminary data from the study, which it called the "Feinman ALT/NANB PTH Study" (that is, the Feinman ALT/non-A, non-B hepatitis post-transfusion hepatitis study).

The position paper recommended that the Red Cross "delay testing and design a pilot study that will take into consideration Dr Feinman's data in Toronto recipients." It said that the American Red Cross's council of directors had recommended against introducing anti-HBc testing, and that the American Association of Blood Banks and the Council of Community Blood Centers had decided against surrogate testing. The same statement was made in a letter from Dr Perrault to Dr Leclerc-Chevalier on 3 March 1986. Despite the positive comments about anti-HBc testing made by its medical directors' council in December 1985, the American Red Cross's official position was to reject it. However, that was not true of the American Association of Blood Banks. The association's board had decided, at a meeting on 31 January 1986, to defer consideration of the issue until April, when it hoped that additional information would be available. The position of the Council of Community Blood Centers is less clear, although there is no evidence that it had rejected surrogate testing. Dr Thomas Zuck, a blood banker in the United States and a past president of the council, testified that, unlike the association, the council was not a standard-setting body. In fact, many of the council's members were also members of the American Association of Blood Banks and, by the spring of 1986, were conducting ALT testing on a routine basis. The position paper also said that the U.S. Food and Drug Administration had rejected the recommendation of its blood products advisory committee for implementation of both ALT and anti-HBc testing. Although the administration had not ordered the implementation of those tests by regulation, and did not need to because the blood bankers had acted voluntarily, it had not rejected the recommendation. Indeed, in 1987 it facilitated the

implementation of surrogate testing by conducting a workshop to resolve outstanding issues related to its implementation. After this workshop, the major blood-banking agencies continued with surrogate testing.

By the time the medical directors of the Canadian Red Cross met on 19–21 March 1986 and discussed the position paper, there had been yet another change in the American Red Cross's position. It had decided to implement both surrogate tests. The medical directors were told of that decision and that the U.S. Food and Drug Administration's blood products advisory committee had recommended the implementation of both surrogate tests. According to the minutes of the meeting, the medical directors recognized that, with the major U.S. blood organizations moving to surrogate testing, "pressures would be very high" for the Canadian Red Cross "to do something."

The medical directors were told that the surrogate tests using ALT and anti-HBc had a combined predictive value of only 12 per cent, which meant that 88 per cent of the units discarded would be discarded needlessly. The minutes do not record any mention of the fact that it was also predicted that these tests would prevent as much as 60 per cent of cases of post-transfusion hepatitis. They were also told that the preliminary data from the Toronto incidence study as of July 1985 showed 7.6 per cent of transfusion recipients developing non-A, non-B hepatitis. This incidence was comparable to that in many parts of the United States where surrogate testing was being implemented. Dr Perrault said that the "preferred position" for the Canadian Red Cross was further study. Although there was no consensus among the medical directors, Dr Perrault said at the meeting that his position would be set before the advisory committee of the blood transfusion service and, if supported there, would be presented to the board of directors of the Canadian Red Cross and to the Canadian Blood Committee.

The advisory committee met on 18 April 1986. For it, Dr Perrault revised the position paper originally written for the medical directors. The statement that the three major voluntary U.S. blood organizations had rejected anti-HBc testing was not corrected. Dr Alfred Katz, the executive director of blood services of the American Red Cross, was present and reported that his organization would implement both surrogate tests, but the advisory committee was not told that the American Association of Blood Banks had also recommended the implementation of both surrogate tests. Nor did the revision correct two other statements in the original position paper, that the Food and Drug Administration had rejected the recommendation of its blood products advisory committee, and the implication that the Toronto incidence study would examine the efficacy of ALT testing. In testimony, Dr Perrault disagreed with a suggestion that he had left erroneous impressions regarding these matters.

The revised position paper reported that, at their meeting in March, the Red Cross medical directors had considered the possibility that HIV testing "may well be a good surrogate test of its own." In an attached document, data were provided about the number of HIV-antibody-positive donors who had excluded themselves in a pilot study at the Toronto centre. Dr Perrault suggested in the position paper that HIV-antibody testing and self-exclusion could be considered as surrogate tests for non-A, non-B hepatitis equal to testing for anti-HBc. During his testimony, he agreed that there were no data to support that hypothesis at that time.

The revised position paper given to the advisory committee contained the same statements about the Toronto incidence study that were in the original version and had the same attached data, again titled the "Feinman ALT/NANB PTH study." Dr Perrault said that the medical directors had recommended that further data be gathered. The revised position paper also stated that "Dr Feinman's study (July 1985 data attached) is not yet complete, in particular testing of all stored samples for anti-HBc has yet to be undertaken." There had been no previous mention of any intention to conduct anti-HBc testing as part of the Toronto incidence study. In response to a question during his testimony, Dr Perrault said that, although there had never been a plan, it had been a possibility. Unlike ALT testing, anti-HBc testing could in fact have been conducted on the samples that the Red Cross had agreed to give to the investigators of the Toronto incidence study, although no such testing occurred.

The advisory committee recommended unanimously that

the Canadian Red Cross Society should not take steps to implement surrogate tests for non-A, non-B hepatitis until:

- a) further data have been gathered on the value of such testing in the Canadian context (that is, until the Feinman study has been fully assessed), and
- b) the impact of testing for HTLV-III [HIV] antibody and the process of "self-designation" that is being assessed at Toronto Centre have been considered as possible surrogate tests for non-A, non-B hepatitis.

In the interim, international data should be reviewed in order to assist with media inquiries.

That recommendation was adopted by the Red Cross's board of directors at its meeting on 26 May 1986.

At the request of Dr Perrault, the issue of surrogate testing for non-A, non-B hepatitis was then placed on the agenda of the Canadian Blood Committee's advisory subcommittee, which was scheduled to meet on 19 June 1986. For that meeting, the Red Cross prepared a new position paper. It reported that, since the blood transfusion service advisory committee meeting in

April, the American Association of Blood Banks had announced that both ALT and anti-HBc testing would be incorporated into its standards. It did not, however, explain that the association's announcement came in a joint statement with the American Red Cross. It said that the Canadian Red Cross remained unconvinced of the effectiveness of the surrogate tests and was preparing a cost-benefit analysis. It included the preliminary data from the Toronto incidence study and a statement that only twenty cases of post-transfusion hepatitis were reported to the Red Cross every year.

During this meeting Dr Perrault repeated the comment that he had made to the blood transfusion service advisory committee, that "the documentation indicates that AIDS testing can be a good surrogate test for non-A, non-B hepatitis." He also told the Canadian Blood Committee advisory subcommittee that a "study was being carried out at Mount Sinai which included ALT testing" and that additional "research on anti-HBc should provide indications on whether such surrogate tests are scientifically valid."

The position paper prepared for the Red Cross blood transfusion service advisory committee had estimated the cost of implementing both surrogate tests as between \$5 million and \$8 million per year. The position paper prepared for the Canadian Blood Committee advisory subcommittee estimated the cost of implementing surrogate testing in Canada as at least \$5 million per year, and during the meeting Dr Perrault said that the cost could easily reach \$10 million. These estimates appear to be based on the expected cost of the test kits, and did not take into account additional costs, such as the cost of recruiting new blood donors to replace those who would be deferred as a result of testing.

A more detailed analysis of the cost of implementing surrogate testing was prepared by the Red Cross several months later and was presented to the medical directors when they met in September 1986. The estimate had grown to \$19.941 million for the first year, allocated as follows: \$6.715 million for test kits; \$2.356 million for additional staff and staff training; \$9 million to recruit and collect donations from new donors (assuming that 5 per cent of donors would be deferred as a result of the testing and a cost of \$150 per donor); \$1.12 million for additional data management systems; \$750 thousand for renovations to the blood centres. Some of these costs were one-time costs that would be incurred only in the first year, although the estimate did not identify which fell into this category or give an estimate of the annual cost of surrogate testing in subsequent years.

The Red Cross also prepared an estimate of the costs that would result from surrogate testing to the health care system and employers during the first year. They were predicted to be more than \$66 million, consisting of \$45 million for medical follow-up to 60,000 deferred donors (also based on a 5 per cent deferral rate) and a cost to employers of \$21.6 million in lost work (based on an estimated three days of work lost for each employee who was deferred as a donor, at a rate of \$15 per hour). The method and models used

in developing these estimates were not explained, nor were sources given for the figures on which they were based. These estimated costs of surrogate testing did not take into account the medical, economic, or societal costs that would be saved by a reduced incidence of post-transfusion non-A, non-B hepatitis if surrogate testing were implemented.

Cost, without recognition of the benefits of testing, continued to dominate the discussions during the next three years about whether to implement surrogate testing in Canada. The estimates varied greatly, often with little or no explanation about what they included or how they were arrived at.

On 12 July 1986, the *New York Times* published a report about the incidence of post-transfusion non-A, non-B hepatitis in the United States in which it referred to the implementation of surrogate testing by the major U.S. blood-banking organizations. Because that report was likely to attract attention to the issue in Canada, Dr Perrault wrote a memorandum five days later to the commissioners and directors general of the provincial divisions of the Red Cross that included the following statements:

6. Currently the American Red Cross and some other volunteer blood collection agencies are introducing one or both tests on a trial basis in an attempt to determine if this would reduce the incidence of Non-A and Non-B hepatitis.
7. Testing blood for this index of possible viral infectivity is not universally underway in the United States at the present time.
8. The Canadian Red Cross Society is monitoring these developments closely and is in direct contact with the agencies conducting the trial studies.
9. However, there is no intention of introducing this experimental approach in Canada until more conclusive evidence of its effectiveness in reducing the incidence of this type of hepatitis becomes evident.

In discussing the article with employees of the Canadian Blood Committee, Dr Perrault said that the "basic approach of the CRCS [Canadian Red Cross Society] at this time is that the American situation is different from the Canadian one, and our current occupation is to gather data on the matter." This, he testified, was a reference to awaiting the final results of the Toronto incidence study.

The decision of the major American blood-banking organizations to implement surrogate testing was not a trial, as Dr Perrault described it in his memorandum, nor was surrogate testing still experimental. Anti-HBc testing was not yet universal in the United States because a transition period was needed and the American Association of Blood Banks had extended its deadline for implementation accordingly. Nevertheless, ALT testing was nearly universal by this time, as Dr Zuck, who was then director of the division of blood and blood products of the U.S. Food and Drug Administration, testified. Dr Perrault

was asked during his testimony why he had characterized the implementation of anti-HBc testing in the United States as he did. He said that that had been his understanding at the time. Dr Perrault's description of the state of surrogate testing in the United States was also used by other persons within the Canadian Red Cross.

Canadian study of surrogate testing, 1986–7

The proposal for a multicentre study of the incidence of post-transfusion hepatitis in Canada, made in March 1984, was revived more than two years later. In 1984, the Red Cross had decided that it did not need to conduct such a study because of the existence of Dr Feinman's study of the incidence of post-transfusion hepatitis in Toronto. In 1986, the Red Cross's position changed, beginning at a meeting of the medical directors on 28 September. The minutes of that meeting record criticism of the design of the Toronto incidence study:

J. Nusbacher [the medical director of the Toronto blood centre] said that the Feinman study lacked a control group and information on donors, and recommended that a prospective study be done on elevated transaminase [ALT]. This will be taken up by the Transmissible Diseases Working Group in collaboration with Laboratory Services.

Although Dr Nusbacher's comments about the Toronto incidence study were correct, the Red Cross had long known the design of the study and its limitations. It was the Red Cross's own limitations in identifying and testing blood donations sent to Mount Sinai Hospital that had made it impossible for Dr Feinman to evaluate the use of ALT as a surrogate test for non-A, non-B hepatitis.

Only a few months earlier, in April 1986, the advisory committee of the Red Cross blood transfusion service had recommended that no steps be taken to implement surrogate testing until the data from the Toronto incidence study were fully assessed. For the meeting at which that recommendation was made, the committee had been given a position paper that implied that the Toronto incidence study would also produce data on the efficacy of ALT testing as a surrogate test for non-A, non-B hepatitis. At that meeting, Dr John Furesz, the director of the Bureau of Biologics, the federal regulatory body, asked how long the Red Cross proposed to gather data. Dr Perrault replied that a report would be made at the next meeting of the advisory committee. The next meeting was held on 7 November 1986. When Dr Furesz asked then about the Toronto incidence study, Dr Perrault reported that it "had not been well designed [because] only ALT status was examined, not anti-HBc" and that "the experiment was not adequately controlled." Dr Perrault proposed to the advisory committee that a multicentre study be conducted.

Such a proposal had already received support, on 17 October, from the transmissible diseases and immunology working group, a Red Cross committee that had taken over much of the work of the former hepatitis working group. The new working group recommended that the Red Cross collaborate with the Canadian Liver Foundation, the Laboratory Centre for Disease Control, provincial laboratory services, and federal and provincial health agencies in a study of the incidence and prevention of non-A, non-B hepatitis in Canada, including post-transfusion cases, and of the use of anti-HBc and ALT as surrogate tests. This suggestion led to the formation of an ad hoc study group on testing for non-A, non-B hepatitis, consisting primarily of representatives of the Red Cross and the Canadian Liver Foundation. That group met on 9 April 1987 to consider a draft study protocol prepared by Dr Mabel Halliday of the Canadian Liver Foundation's epidemiology unit.

Dr Halliday's proposal did not go forward, at least in part because of the proposed cost – an estimated \$8.5 million over two years. Dr Davey sent a preliminary draft of the research plan to McMaster University's department of clinical epidemiology and biostatistics for analysis and for advice on a "less expensive alternative," with the following comment:

The evident difficulty is the so-called bottom line: an estimate of \$8.5 million over two years! This is nearly half the annual funds available to the NHRDP [National Health Research and Development Program] and about 5 per cent of total MRC [Medical Research Council] funding. Canadian support to this extent is so far from likely that the study as proposed would have to seek U.S. support, presumably from NIH [U.S. National Institutes of Health]; and even for them it's a large amount.

It was then suggested to Dr Morris Blajchman, the medical director of the Hamilton blood centre and a professor in the faculty of medicine of McMaster University, that he draft another proposal. On 8 October 1987, Dr Blajchman wrote to Dr Perrault that he was working with other experts in preparing a proposal for a randomized study of the value of surrogate testing to prevent non-A, non-B hepatitis. On 28 October, Dr Perrault told the Canadian Liver Foundation that the Red Cross would not support Dr Halliday's protocol.

During the previous several months, support for a major study in Canada had come from the United States. As is discussed in the previous chapter, the interventionist study which had been discussed for so many years in the United States had been precluded there by the introduction of surrogate testing. Interest in such a study did not disappear, however, and encouragement for a Canadian study was given by several U.S. experts in post-transfusion hepatitis. Dr Alfred Katz, the executive director of blood services of the American Red Cross, attended a meeting on 7 November 1986 of the advisory committee of the Canadian Red Cross blood transfusion service and expressed the opinion that the multicentre study afforded the Red Cross

"an opportunity to do something very important." Dr Harvey Alter, the principal investigator of the NIH study, had spoken to the same effect at the workshop held by the U.S. Food and Drug Administration in January 1987 to discuss problems in the implementation of surrogate testing for non-A, non-B hepatitis. By that time, the final results of Dr Feinman's Toronto incidence study were known to experts in the United States. At the workshop Dr Alter said:

Whether or not the United States chooses to go with anti-core, there will be some areas of the world where this test will not be done. I speak particularly of Canada, where that decision has already been made. The key missing element since 1981 which has made this decision process so agonizing has been the lack of a controlled prospective study to determine if the predicted efficacies could be actualized in practice. I would urge that one of the outcomes of our deliberations be a commitment by NIH and the major blood organizations of the United States and Canada to jointly fund a proper multicenter controlled prospective study of surrogate tests in the prevention of non-A/non-B.

... the proximity of the U.S. and Canada, the similarity of the populations, to a certain extent at least, make it a fertile area to do the proper studies. At least in Toronto, the incidence of non-A/non-B in a study just completed was 9.1 per cent – very similar to the findings in the U.S. ...

We have been given this gift of Canada, if you will – of a similar population, with contiguous borders, where it would be easy to go back and forth. I think it would be just a tragedy, even if we are doing the tests, not to look at it in a similar population where they are not doing the tests ... It will take three or four years. It will be very expensive. That is why I thought it would pay for groups to combine in funding this.

Dr Alter's support for a Canadian study was relied on by the Red Cross, but the context of his remarks was overlooked. In response to discussions about whether such a study would be ethical in Canada, Dr Alter said:

I just wanted to clarify what I'm saying about a controlled study. First of all, I am not rejoicing in Canada's decision, and I think Canada, although this will allow us, perhaps, to do the study that I wanted, I think the decision in Canada is not one I would agree with, in that they should be doing at least one of the surrogate tests.

But be that as it may, they have already decided not to do either of these tests.

Dr Alter's support for a Canadian study was premised on his understanding that a decision not to do either surrogate test had already been made in Canada.

Similar backing of a Canadian study was given by two prominent U.S. hepatologists in an editorial in the journal *Gastroenterology* in August 1988. Their position was also premised on the similarity in the incidence of post-transfusion non-A, non-B hepatitis in Canada and the United States and the understanding that the Canadian Red Cross had already decided not to implement surrogate testing.

In Canada, the proposal for a multicentre study also received considerable encouragement. It had been endorsed first by the Canadian Blood Committee's advisory subcommittee at a meeting on 14 October 1987. The Red Cross had not asked that the study be discussed in that venue, but the topic had been raised by Dr Gershon Growe, the director of the Vancouver General Hospital blood bank and a physician treating hemophiliacs. Dr Growe had been concerned about surrogate testing for several months and, in July 1987, had written to the medical director of the Red Cross blood centre in Vancouver describing Canada's response to surrogate testing as "sluggish" and a "travesty." Dr Growe told the subcommittee that there was a consensus in the United States that the data from the TTV and NIH studies, "although imperfect, supported the conclusion that testing donor blood for both ALT and anti-HBc would be effective in reducing non-A, non-B hepatitis significantly." Dr Brian McSheffrey, the medical director of the Saskatoon blood centre, who was the acting national director of the blood transfusion service, said that, if funding were not available to conduct the study within one year from the date of the meeting, the Red Cross should proceed to implement surrogate testing. The subcommittee agreed that the Red Cross should proceed with the development of a research proposal on the understanding that, "if such a study were not feasible within a reasonable time, consideration would be given to the possibility of implementing surrogate screening, subject to Canadian Blood Committee approval, given the high cost for the testing." Three months after the advisory subcommittee meeting, Dr Growe wrote to Dr McSheffrey that, although he felt that Canada was "somewhat sluggish in getting off the mark," he was "happy to see that something was being done"; he hoped that preliminary results would be available within the next year in order to implement testing if necessary.

The Canadian Blood Committee, on which all the provinces were represented and which was concerned principally with the funding of the blood program, was aware of the proceedings of its advisory subcommittee. At a meeting of the full committee on 16 October 1987, the view was expressed that those countries which were implementing surrogate testing were responding to "non-scientific pressure," and that Canada had an opportunity to assess the reasonableness of surrogate testing "before facing the considerable financial consequences." The committee's implicit support for further study was conveyed by its executive director, Dr Leclerc-Chevalier, to a meeting of Red Cross medical directors on 16 November 1987. On the day after the meeting, Dr Leclerc-Chevalier recorded in a memorandum to file

that the Toronto incidence study had found evidence of post-transfusion non-A, non-B hepatitis in more than 9 per cent of recipients, that one-third of these patients (3 per cent of all recipients) would develop chronic hepatitis, and of this group 10 per cent would develop cirrhosis within ten years. She described the status quo as politically unacceptable; pressure was expected to increase further as other countries implemented or considered testing. Her memorandum indicates that the proposed study was expected to cost \$2 million, and that this was one-eighth of the estimated first-year cost of full implementation of the two surrogate tests.

At the meeting on 16 November, the medical directors supported further study, on the understanding that they might have to proceed with the implementation of surrogate testing "if political, legal, or manufacturing pressures necessitate quick action."

Consideration by the Canadian Hemophilia Society

On 6 October 1986, Dr Martin Inwood, who was both a physician who treated hemophiliacs and the representative of the Canadian Hematology Society on the Canadian Blood Committee's advisory subcommittee, proposed to the advisory subcommittee that an ad hoc subcommittee be formed to address "issues regarding [the] safety of current concentrates available in Canada." The proposal was for a multidisciplinary group that would serve as a forum for matters requiring continuing review, including whether all Canadian plasma for concentrate production should be tested using ALT, HBc antibody testing, or both. The chair of the committee said that he would raise the issue at the next meeting of the Canadian Blood Committee for it to consider. The committee's next meeting was held on 3–4 February 1987, but Dr Inwood's proposal was not discussed.

On 7 April 1987, the medical, scientific, public health issue committee, a committee of the Ontario chapter of the Canadian Hemophilia Society, decided that the best factor concentrate for use by hemophiliacs was made from plasma "pre-screened for HIV and NANB hepatitis, and then vapour heated." On 27 April, the committee wrote to the Canadian Hemophilia Society's representative on the Canadian Blood Committee demanding that all factor concentrates be made from plasma screened using surrogate tests:

Many U.S. blood banks have now instituted screening for one or both of these surrogate NANB markers. Why are all plasma sources for use by Canadian hemophiliacs not similarly screened in an effort to reduce or eliminate NANB hepatitis? ... Is it not time to err on the side of caution and insist on products that appear to be safer, or put another way, **to stop using our children as the miners canary! ... We demand self-sufficiency in thoroughly screened (for HIV antibody and NANB surrogate markers) source plasma for all human derived blood products within one year.** [Emphasis in original.]

The same day letters were sent by the committee to the chairs of the medical and scientific advisory committees of both the Canadian Hemophilia Society, its Ontario chapter, and the Ontario Hemophilia Centre directors group, asking that ALT and anti-HBc testing of plasma for fractionation be placed on the agenda of a series of meetings of these committees to be held on 1–2 May 1987.

Surrogate testing was discussed at these meetings. Based on a fact sheet prepared by Dr Irwin Walker, the medical and scientific advisory committee of the Ontario chapter concluded that surrogate testing would prevent from one-half to two-thirds of post-transfusion non-A, non-B hepatitis, at a loss of 8 per cent of blood donors (2 per cent ALT, 6 per cent anti-HBc). The committee concluded that, because the tests are only partially effective, "it is likely ... that large pooled samples would continue to be contaminated with the plasma from donors carrying undetected non-A, non-B hepatitis." The national medical and scientific advisory committee, which met on 2 May 1987, agreed that ALT and anti-HBc testing might contribute to the reduction of non-A, non-B hepatitis. Neither committee recommended the adoption of surrogate testing in Canada. According to Dr Davey, who had attended the meeting of the national advisory committee, surrogate testing was "not considered a pressing issue by the medical and scientific advisory committee although it may be by other members of the Canadian Hemophilia Society."

Although by itself ALT testing of plasma for fractionation was not likely to reduce the risk of transmission of non-A, non-B hepatitis by concentrates, it was hoped that when used in conjunction with viral inactivation methods the risk would be significantly reduced. Steam and wet heat treatment, developed in the mid-1980s, had been shown to be effective in inactivating the causative agent or agents of non-A, non-B hepatitis. At the medical and scientific advisory committee's annual meeting in May 1986, one physician reported that he had begun using a wet heat-treated product obtained through the Health Protection Branch's emergency drug release program to treat a young hemophiliac previously unexposed to blood products. On 20 May 1986, the chair of the Canadian Hemophilia Society's medical and scientific advisory committee wrote to the Red Cross to request formally that the Red Cross make wet heat-treated factor concentrates available to "naïve hemophiliacs" who had never been treated with blood products and to those hemophiliacs who were to participate in a clinical trial of wet heat-treated concentrates. The committee also requested that wet heat-treated products be made available to naïve hemophiliacs who for some reason would not be participating in the clinical trial, and to mild hemophiliacs with normal ALT levels then being treated with cryoprecipitate but who on the advice of their physicians planned to switch to concentrates. On 16 June 1986, the Red Cross agreed to distribute wet heat-treated products for use by naïve hemophiliacs whether or not they were enrolled in the clinical trial, but not to the hemophiliacs who had been using cryoprecipitate.

Surrogate testing of Canadian plasma and the availability of wet heat-treated products were the principal issues to be discussed by a proposed scientific symposium and consensus conference on safety and security of blood products that had grown out of the original proposal to the Canadian Blood Committee for an ad hoc advisory subcommittee. Originally proposed for November 1987, the consensus conference was not held until February 1988. By this time, it was known that Canadian hemophiliacs had contracted HIV while using dry heat-treated concentrates, and a decision to convert to wet heat-treated factor concentrates had already been taken. On 1 February 1988, the acting national director of the Red Cross blood transfusion service wrote to Dr Gershon Growe, a physician who treated hemophiliacs and who had expressed concern that surrogate testing had not been implemented, that it was hoped that the use of wet heat-treated factor concentrates would "settle" the problem of non-A, non-B hepatitis "from the point of view of the hemophiliacs." The consensus conference held on 11 February 1988 dealt primarily with wet heat-treated concentrates, and surrogate testing was dealt with only briefly in a question. (A detailed discussion of the conversion to wet heat-treated factor concentrates is found in Chapter 16.)

Position of the Bureau of Biologics

Until the autumn of 1987, the Bureau of Biologics, the federal body regulating safety in blood products, had not recommended any action with regard to surrogate testing for non-A, non-B hepatitis and had not established an official position on the issue. Representatives of the bureau had, however, attended meetings of various committees of the Red Cross and the Canadian Blood Committee at which the subject was discussed. Because the regulations enforced by the bureau did not extend to blood or blood components, it was focused on safety in blood products, such as the factor concentrates on which hemophiliacs depend. In November 1987, surrogate testing became a subject of several memoranda exchanged between Dr Furesz, the director of the bureau, and Dr Wark Boucher, the chief of its blood products division. In these technical and at times confusing memoranda, anti-HBc testing was rejected and ALT testing was characterized as no more than marginally useful.

On 19 November, Dr Boucher wrote to Dr Furesz that four out of nine pools of plasma from Canadian donors that had been sent to Cutter Laboratories Inc. (Cutter) in the United States for fractionation were not being processed because they contained units of plasma from donors implicated in the transmission of hepatitis B or non-A, non-B hepatitis. Furthermore, two lots of factor concentrate already made from Canadian plasma were not being distributed for the same reason. Since the early 1980s, it had been the policy of the bureau to deal with such cases on an individual basis. The disposition of the plasma or product in question, and in particular whether it would be processed for eventual distribution or, if already processed, distributed, would

depend on whether the destruction of the plasma pool or lot would result in a shortage in Canada of factor concentrates. The question had begun to arise more frequently as attention gradually returned to the risk of post-transfusion hepatitis.

Dr Boucher wrote that, if the bureau intended to prevent the distribution of the products, the Red Cross wanted an "official document" to this effect, because "[i]f the CRC [Canadian Red Cross] tells Cutter to destroy these lots, they still have to pay for processing as none of the American companies recognize PTH [post-transfusion hepatitis] as a reason for not issuing a lot." Dr Boucher continued:

Obviously, if we did ALT screening we could at least state that we were at a level of testing (albeit questionable) of the US, UK, Germany, France, etc. The monies which will be lost in destroying lots may in the end equal that which would be spent on ALT testing.

Dr Boucher testified that he believed that, if the then current policies were going to result in the continued destruction of so many lots, it was better to implement ALT testing. Dr Furesz's response was that, although surrogate testing might help in the future, it did not solve the immediate problem; he expressed concern over actions that would "jeopardize" the supply of factor VIII and IX concentrates.

In a second memorandum to Dr Furesz, also dated 19 November, Dr Boucher wrote:

We need to discuss the introduction of ALT testing and anti-core. In my opinion, ALT testing is questionable but harmless. There is a marginal benefit from the introduction of this test.

On the other hand, I believe that the introduction of the anti-core test could result in HBV [hepatitis B virus] contaminated lots of F[actors] VIII and IX. The only lot of F VIII which Cutter has ever found positive for HBV antigen is a lot which was prepared from plasma units which had been screened for anti-core.

Denise [Leclerc-Chevalier] told me that the CRC [Canadian Red Cross] wants to start a pilot project in three or four centres where they will evaluate the effect of ALT and anti-core testing on PTH [post-transfusion hepatitis]. I told her that we have never been informed on what programs the CRC gets involved in and many of these may or could affect the final products produced from plasma. I told her that in my opinion, anti-core testing was a hazard and that if products were to be prepared from plasma units with no or low levels of antibodies to HBV then we would require that the starting material should contain plasma with high titers [amounts of antibodies] to HBV to ensure that HBV is not transmitted.

Dr Furesz replied that he agreed with Dr Boucher and asked whether the United States used both tests.

In describing anti-HBc as a hazard, Dr Boucher was referring only to fractionated products which, unlike components, are derived from many donors whose plasma is pooled. When a person is infected with the hepatitis B virus, it is the antibodies to the hepatitis B surface antigen (anti-HBs) that neutralize the virus and confer a protective benefit. The protective effect of anti-HBs can occur even when many units of plasma are pooled together before being manufactured into blood products, and can thus reduce the infectivity of any hepatitis B-positive units in the pool that may have escaped detection by regular testing. In addition, some blood products, such as immune globulins, require a certain level of anti-HBs to be effective. Because anti-HBc and anti-HBs exist in the bloodstream at approximately the same time, removing donations containing one inadvertently removes the other.

In a third memorandum, dated 20 November, Dr Boucher wrote that the Toronto incidence study had found a 9 per cent incidence of post-transfusion non-A, non-B hepatitis. He said that he was being conservative in calculating that, if one were to estimate that only 5 per cent of the plasma units used in the manufacture of factor concentrates were infectious with non-A, non-B hepatitis, 740 units of a 3,700-litre pool (14,800 donations) would be infectious. He concluded:

Thus if we find that one unit is implicated in PTH [post-transfusion hepatitis], there are still 739 units which contain NANB. Even if we do screen for ALT, we would reduce the incidence by one-half at best. I think that we should allow these pools [that is, the suspect ones at Cutter Laboratories Inc.] to be used and that we should require or strongly recommend that CRC start ALT testing. This is one point which I may raise with the CBC [Canadian Blood Committee]. I will tell them that legal opinion is that we have to be "state of the art" whatever that means in this instance.

Although there is no record of Dr Furesz's response, it is clear from subsequent events that the bureau did not require, or recommend, that the Red Cross implement ALT testing of plasma destined for manufacture into blood products. When asked why, both Dr Furesz and Dr Boucher referred to the decision to begin a Canadian study of the value of surrogate testing.

The bureau's position was presented by Dr Boucher at a meeting of the Canadian Blood Committee on 8 December 1987. He said that "blood lacking HB core antibody may be more hazardous than blood containing it ... unless the valuable hepatitis B antibodies could be maintained in the plasma pool." He also said that the bureau would not require surrogate testing unless there was "clear and tangible proof of increased protection." No distinction was made in the discussion between plasma for fractionation and blood components for transfusion. The background materials for the meeting show

that the bureau was obtaining legal advice on whether surrogate testing should be implemented. The chair of the Canadian Blood Committee said that the committee might eventually feel forced to support the implementation of surrogate tests from the “political and litigation points of view.”

The Canadian multicentre (Blajchman–Feinman) study

In designing and conducting the multicentre study, Dr Blajchman collaborated with Dr Feinman, who had had experience in studying post-transfusion hepatitis as the principal investigator of the Toronto incidence study. They proposed two objectives: first, to determine whether withholding units of donated blood that tested positive for the surrogate markers (anti-HBc and elevated ALT) could reduce the frequency of post-transfusion non-A, non-B hepatitis and, second, to determine the background incidence of non-A, non-B hepatitis by following a group of patients who had deposited their own blood for transfusion before undergoing elective surgery and had received no other blood in treatment.

The study would involve both emergency patients and those scheduled for elective surgery. Patients would be excluded if they had a history of liver disease or alcohol abuse, had received a transfusion in the preceding six months, were at high risk of contracting hepatitis B, or had a pre-transfusion ALT level greater than 1.5 times the upper limit of normal. Emergency patients who were unable to give their informed consent to participation before surgery would be asked to consent within twenty-four hours of any transfusion.

The study participants were to be divided into two groups. One group would receive blood components that had reacted negatively to the Red Cross’s usual tests. The other group would receive blood components that were not only negative for the usual tests but were also normal in ALT level and anti-HBc negative. No one would know which patient received which kind of blood component until the results were analysed. Patients would be considered to have post-transfusion hepatitis if

- within two to twenty-four weeks of transfusion, they developed an ALT level 2.5 times the upper limit of normal;
- seven to ten days later, their ALT level was still two or more times the upper limit of normal; and
- all other potential causes of liver dysfunction were excluded.

This study was similar to Dr Halliday’s proposal, but it differed in the choice of participating centres. Dr Halliday planned to use centres in three cities known to have a substantial prevalence of hepatitis – Montreal, Vancouver, and Toronto. The Blajchman–Feinman study would use centres in Toronto, Hamilton, and Winnipeg. Of these, only Toronto was known to have a high prevalence of hepatitis. The prevalence of hepatitis in the general population

of a selected centre was significant for the success of any study. The incidence of post-transfusion hepatitis would be influenced by the prevalence of hepatitis in the general population; a low rate of post-transfusion non-A, non-B hepatitis could be expected in a centre with a low prevalence of non-A, non-B hepatitis generally. For the results of the study to be valid, it would have to include a statistically significant number of transfusion recipients who had developed post-transfusion non-A, non-B hepatitis. The lower the number of occurrences of post-transfusion non-A, non-B hepatitis among the patients in the study, the longer it would take for the study to be completed. The choice of Hamilton and Winnipeg ultimately proved important because the lower-than-expected incidence of post-transfusion non-A, non-B hepatitis contributed to many delays in completing the study and to its increasing cost.

The exclusion of Vancouver from the study concerned Dr Growe, the director of the Vancouver General Hospital blood bank, and Dr Noel Buskard, the medical director of the Red Cross's Vancouver blood centre. They believed that, because of the high prevalence of hepatitis in Vancouver, that city had a special interest in the study and could offer the substantial number of patients needed to complete it without delay. In January 1988, in the same letter in which he said he was "happy to see that something was being done," Dr Growe wrote to Dr McSheffrey, the acting national director of the blood transfusion service, as follows:

Looking at the distribution of the centres that are participating in the trials gives me some concern, however, and I felt that possibly Vancouver should be included in the group of test sites for several reasons. One reason is of course that there is a significant interest in this center in the whole issue and therefore co-operation would be good. And the second major reason is that we have a certain ethnic mix out here which is probably different certainly from Winnipeg and Hamilton. That is we have a large number of orientals [there being a high prevalence of hepatitis in Asia] proportionally, and also we have the largest proportion of gay men. It may very well be that the pilot study would show that non A, non B screening would be appropriate in certain parts of Canada and not in others, but if high-risk areas are not surveyed in your initial review then we will never know.

Dr Blajchman responded that the study was designed only to examine the value of surrogate testing in reducing the incidence of non-A, non-B hepatitis and that it should not matter where the study was done to answer that question.

Appraisal and revision, May 1988–May 1989

It was hoped that the Canadian multicentre study would be made possible by a grant from the National Health Research and Development Program, which operated within the Department of National Health and Welfare and

was concerned primarily with research about health care delivery. Dr Leclerc-Chevalier arranged to have the approaching deadline for applications for funding by the program extended to 20 December 1987. The decisions about the application would not be made until May 1988, however, and to avoid delay the Red Cross provided \$200,000 in temporary funding to cover the cost of the study from January 1988 to May 1988. This funding was approved on the understanding that it would be recovered from the Canadian Blood Committee or funded by the National Health Research and Development Program. At the time, the study was expected to cost \$2 million and to last a minimum of nine to twelve months. In fact, funding was not approved until September 1989. Several factors contributed to the delay in funding. They included criticisms of the study by reviewers, concerns about patients' consent, and, finally, the high cost of the study.

In any application for funding for scientific research, it is normal to send the proposal to experts in the field, who are asked to review such matters as the design, the competence of the investigators, and the significance of the study. The staff of the National Health Research and Development Program sent the proposal for the Blajchman-Feinman study to the program's own blood products review committee, which was made up of experts in related fields, and to external experts selected by that committee. The reviews were positive; the study was described as "extremely important," "valuable for making blood donor screening policy," and "vitally needed." There were, however, specific reservations about the need for a control group to measure the background incidence of non-A, non-B hepatitis, about the required sample size, which was said to be too small, and about the definition of non-A, non-B hepatitis that would be used. According to the review committee, the proposal "created a unique situation in which there was virtual unanimous approval of the science and need but rejection of the validity of the methods." On 7 July 1988, the committee recommended that the investigators revise and resubmit their proposal. Because of the significance of the study, it also recommended that a revised proposal be dealt with quickly after it was submitted.

One of the issues identified by the review committee related to an announcement made in May 1988, while the original proposal was under consideration. A biotechnology corporation, Chiron Corporation, announced in that month that it had isolated and cloned proteins from the virus responsible for non-A, non-B hepatitis. The virus it identified was later called the hepatitis C virus, or HCV. Although a commercial test would not be available immediately, and the extent to which HCV was responsible for all post-transfusion non-A, non-B hepatitis was still unknown, the discovery could affect any decision about the need for surrogate testing. Several reviewers raised the possibility of including tests for the antibody to HCV in the study.

A revised application was submitted on 25 October 1988. It did not satisfy all the program's requirements. In particular, it did not meet the Medical Research Council's ethical guidelines for research, which required patients

to consent to participate in any such study before they received a transfusion that would be part of the study. The Blajchman-Feinman study had provided for post-transfusion consent in cases of emergency surgery. That procedure was acceptable to the ethics review committees of at least some of the hospitals that were to participate in the study, which had reviewed the study originally. They reasoned that the patients in the study who received blood that had been tested for ALT and anti-HBc might be at lesser risk of acquiring non-A, non-B hepatitis, but that the other patients in the study would be receiving the standard blood for transfusion and so would not be placed at greater risk than usual by participating in the study. The study's investigators were reluctant to require pre-transfusion consent in all cases, because that would exclude patients who needed blood for emergency surgery and thereby lengthen the time needed to achieve a sample large enough for statistically significant results.

The timing of patient consent was considered by lawyers of the Department of National Health and Welfare, who "strongly advised against anything other than early informed consent" and stressed that the study must be "above criticism." Based on this opinion, Dr Ian Henderson, the assistant executive director of the Canadian Blood Committee, wrote to the National Health Research and Development Program, in a memorandum dated 17 November 1988, that "there is no substitute for pre-transfusion informed consent, which clarifies the better benefit:risk ratio of joining the trial as compared to receipt of standard untested blood." In a subsequent memorandum, Dr Henderson indicated that he had also consulted with representatives of the Medical Research Council's standing committee on ethics, and that they also believed that informed consent to participation in the study should be obtained before any potential participant received a transfusion.

In December 1988, it was proposed that the study's investigators, the chairs of the hospital ethics committees at each of the hospitals participating in the study, and representatives of the National Health Research and Development Program meet to try to resolve the issue. On 25 January 1989, Dr Feinman and Dr Blajchman wrote to the Extramural Programs Directorate, the office within the Department of National Health and Welfare that administered the National Health Research and Development Program. They repeated their view that post-transfusion informed consent was sufficient, but said that they would be prepared to carry out the study using only pre-transfusion consent, provided additional funding was made available. The extra funding would be necessary because the study would take longer.

The meeting proposed in December was held four months later, on 3 April. It was attended by Dr Blajchman, Dr Feinman, Ms Sheena Lee, the director of research administration within the Extramural Programs Directorate, Dr Henderson, and representatives of the various hospital ethics committees. It was agreed that an information letter would be provided to all patients

who might require a transfusion when they were admitted to hospital. Pre-transfusion consent would be sought when it was feasible to do so, but in emergency situations consent could be obtained afterwards, provided the patient had been made aware of the study upon admission to hospital. On 1 May 1989, the final wording of the information to be given the patient was submitted to the National Health Research and Development Program. It included the following statements:

[T]he blood you will receive will have passed all the Canadian Red Cross Society's tests and, in some instances, may also have passed the additional tests which we are evaluating.

The blood which has passed the additional tests is at least as safe as, and possibly safer, than the standard blood issued by the Canadian Red Cross Society.

On 8 June, the program's blood products review committee recommended the approval and funding of the Blajchman–Feinman study with one proviso – “[t]hat the Canadian Red Cross BTS [blood transfusion service] does not institute surrogate and Chiron testing [for HCV antibody] during the recruitment phase” because “to begin such testing without evidence of need would be wasteful of resources.” It also recommended that the study be reviewed at the end of one year.

More than a year and a half had passed since the Canadian Blood Committee advisory subcommittee had recommended, in October 1987, that, if it was not feasible to complete the multicentre study within a reasonable time, the possibility of implementing surrogate screening should be considered. The study had not yet received final approval, and was not expected to be completed until 1991. Despite this delay, neither the Canadian Blood Committee, which met four times between October 1987 and February 1989, nor its advisory subcommittee considered whether the Red Cross should proceed to implement surrogate testing without waiting for the study's results.

One reason this question did not arise is found in a statement to the committee's advisory subcommittee, at a meeting on 25 October 1988, that “the referee panel of the NHRDP [National Health Research and Development Program] unanimously felt that this study should go ahead prior to a decision to employ routine testing of Canadian blood for the two surrogate markers.” In fact, although the review panel did comment favourably on the need for the multicentre study, all that it had recommended by October 1988 was that the proposal be resubmitted with specific modifications. It had made no recommendation about the implementation of surrogate testing, nor had it recommended that the decision about testing be delayed pending the outcome of the study. Such recommendations would have been well beyond its authority, which was only to recommend whether or not the study merited funding. What the review panel did recommend was that the study be funded

so long as surrogate and HCV antibody testing were not implemented in Canada. This made sense, at least in relation to the surrogate tests, because the very purpose of the study was to determine their efficacy and thus the probable benefits of introducing them. If a decision to implement them was made before the study was complete, further research would be unnecessary.

The review committee had also recommended that any resubmission be considered quickly. In the event, almost another three months passed before federal funding was finally approved and the Red Cross notified in September 1989.

Pressure to implement surrogate testing, 1988–9

From the outset of the Blajchman–Feinman study, it was recognized that circumstances might arise that could require the Red Cross to change its position and implement surrogate testing. This possibility became stronger as financial support for the study was delayed, and on several occasions during 1988 and 1989 events caused the Red Cross to reconsider its policy.

The first was in February 1988, when the Red Cross became aware of an article about surrogate testing to be published in the *Medical Post*, a weekly newspaper for Canadian physicians and other health care workers. The article described surrogate tests as playing “an important part in reducing the incidence of transfusion-induced disease.” It reported statements by Dr Alter, who had led the NIH study, that “while the use of surrogate markers is far from ideal, the lack of any specific test to identify non-A, non-B hepatitis, coupled with the serious chronic consequences of the disease, makes the need for these surrogate tests essential” and that the U.S. decision to implement these tests was “the proper decision.” The article also referred to the Toronto incidence study, the results of which were not yet published, and said it had found an incidence of post-transfusion non-A, non-B hepatitis of 9.2 per cent. Dr McSheffrey, the acting national director of the blood transfusion service, sent a copy of the article to Dr Leclerc-Chevalier, the executive director of the Canadian Blood Committee, with the comment that the article might “raise further demands” for non-A, non-B testing, although in his view it confirmed the need for the Canadian study. The Canadian Blood Committee met a week later, on 9 and 10 February. Dr Perrault said on that occasion that “there is considerable urgency for the study, mainly because considerable public pressure is now forcing the Red Cross into testing, which will be at least ten times more expensive than the controlled trial would cost.”

In the spring of 1988, two statements about surrogate testing appeared in *Vox Sanguinis*, the journal of the International Society of Blood Transfusion. The first reported the implementation of surrogate testing in the United States. The second reported that, in France, the transmissible diseases committee of the national blood transfusion service had recommended that both surrogate tests be implemented. The reasons for the French decision included the following: several prospective studies in France had found that more

than 5 per cent of transfusion recipients – and 70 per cent of hemophilia patients – developed transfusion-related non-A, non-B hepatitis; a randomized study conducted in Lyons had found a highly significant reduction in transfusion-related non-A, non-B hepatitis among recipients of blood from donors with normal ALT levels; the committee considered it possible that anti-HBc testing might further reduce the transmission of hepatitis B from some donors who tested negative for the surface antigen and might also help to eliminate donors at high risk of transmitting other viruses. The French committee believed that the expenses entailed by surrogate testing might well offset the social costs and medical expenses generated by transfusion-related non-A, non-B hepatitis. The article said that an official decision from the French Ministry of Health would soon be made.

By this time Dr Perrault had been appointed deputy secretary general (operations) of the Red Cross. When this report came to his attention on 12 October 1988, he passed it on to Dr Blair Whittemore, now the national director of the blood transfusion service, with the following comment:

In light of the significant delay in patient acquisition in our current study, we must quickly reassess our situation and discuss the issue with the Canadian Blood Committee. At this point, it would seem that we would have no alternative but to begin testing without the benefit of the study. We will await Dr. Blajchman's comments and further action in this matter but I feel that it is important to notify the Canadian Blood Committee at this point.

Dr Blajchman maintained that the Canadian study should proceed because there were no data, "other than this very preliminary French data," that indicated prospectively that surrogate testing reduced the incidence of post-transfusion non-A, non-B hepatitis. He wrote to Dr Leclerc-Chevalier that, if funding was not made available for the study, "then the Canadian Red Cross must start doing surrogate testing."

Pressure to implement surrogate testing was particularly strong in Quebec because of the high prevalence of hepatitis there. On 1 February 1989, Dr Claude Perrault, the chair of a committee made up of the directors of the blood banks of the major hospitals in the Montreal area, wrote to Dr Whittemore. He reported that the committee had passed a resolution that the Red Cross should implement both surrogate tests and gave the following reasons: the frequency with which post-transfusion non-A, non-B hepatitis was occurring; the fact that more than half of post-transfusion hepatitis cases would become chronic; the results of studies showing that ALT and anti-HBc tests would appreciably reduce this incidence; and the international trend towards surrogate testing. On 10 March 1989, Dr Whittemore wrote to Dr Henderson about the delay in funding the multicentre study and told him that "we are beginning to hear some concerns expressed by physicians within the hospital community that we are not addressing this issue in a timely fashion."

In July 1989, Dr Francine Décary, the medical director of the Montreal blood centre, sent Dr Roger Perrault a memorandum which read, in part:

1. I would ask you to reconsider surrogate testing for the CRC [Canadian Red Cross].
2. Hematologists and physicians in the Montreal area are quite worried by the numbers of non A non B hepatitis they are seeing.
3. Moreover, the "Comité des usagers" has written to Blair Whittemore a strongly worded letter asking for the testing (Annex 1) ...
6. I suggest that notwithstanding the Toronto-Hamilton-Winnipeg project, we go ahead in Montreal and test for ALT and anti-HBc.

She added that a private blood bank, which had been established in Montreal for storing patients' own blood before surgery, was testing for both ALT and anti-HBc, and that a regular Red Cross donor had recently been rejected by it because of an elevated level of ALT.

As the pressure mounted, Dr Whittemore came to believe that the Red Cross might have to implement surrogate testing even though a direct test had been developed to detect the antibody to the hepatitis C virus. On 15 May 1989, he told Dr Jo Hauser, who had succeeded Dr Leclerc-Chevalier as the executive director of the Canadian Blood Committee, that the test for HCV should be implemented in a "timely" fashion. He enclosed a recent editorial by Dr Alter, with the comment that, "since there appears to be a long window period between infection and the development of this antibody, Alter has recommended the use of surrogate tests in addition to this specific test." Dr Alter gave three reasons for retaining surrogate testing: the lack of sensitivity of the specific test; the length of the window period; and the possibility that HCV was not the only virus causing non-A, non-B hepatitis. Dr Whittemore also sent Dr Hauser new estimates of the cost of implementing tests for anti-HBc (\$7,233,000), ALT levels (\$3,157,800), and HCV (\$6,208,300), a total of \$16.6 million.

Dr Whittemore's letter, the Alter article, and the cost estimates were circulated at a meeting of the Canadian Blood Committee held on 16-18 May 1989. Dr Hauser said that the Red Cross believed that, "if testing were to be implemented, both the surrogate tests and the direct test from Chiron [for the antibody to HCV] should be used, because the Hepatitis C test will only pick up 50 per cent of the Non-A, Non-B viral agent." After this meeting, Dr Hauser wrote to Dr Whittemore asking him to clarify what he had meant when he said that HCV testing should be implemented in a timely fashion. His letter contained the following questions:

It is my understanding that the Canadian Red Cross Society did not institute surrogate testing because the value of such testing in reducing the incidence of post-transfusion Non-A, Non-B Hepatitis is controversial. Does

the same controversy surround the use of the Chiron Corporation test? Do we have any evidence that this test will reduce the incidence of post-transfusion NANB Hepatitis? If we don't is it reasonable to consider a research project to assess the potential effectiveness of this new test?

You mention in your letter that a specific test for NANB Hepatitis should be introduced in a "timely" fashion. Does this mean "as soon as the experience with its use provides sufficient evidence to justify introducing the test on a wide scale"?

Dr Perrault responded to the letter. He said that HCV testing was not controversial in the way that surrogate testing was, and repeated that "we feel very strongly that this test must be implemented as soon as available."

Dr Perrault and Dr Hauser discussed the mounting pressure to implement surrogate testing on 7 July 1989. Dr Perrault said that the Red Cross intended to proceed with surrogate testing. In a memorandum written a week later to Dr Peter Glynn, the assistant deputy minister responsible for the Health Services and Promotion Branch of the Department of National Health and Welfare, Dr Hauser said:

He [Dr Perrault] has not included the legal arguments for testing in his letter. There is an outstanding suit against the Red Cross concerning non-A, non-B hepatitis which the Red Cross is likely to lose. From a legal perspective the Red Cross has nothing to gain by delaying the initiation of testing. If they delay they are fully liable if it is shown, at some future time, that surrogate testing does prevent hepatitis.

It is clear to me that by recommending that non-A non-B hepatitis testing be implemented the Red Cross is shifting the liability from itself to the CBC [Canadian Blood Committee]. It is likely that the CBC will decide to wait until the results of this project are in. In my view this would be the wise decision – it would allow the research project to proceed to completion and place the liability where it should be – with government.

In his testimony, Dr Perrault denied that the Red Cross really intended to implement surrogate testing. He said that he was trying to convince the government of the need for the study and was just "twisting their arm."

Approval of funding, July–August 1989

The blood products review committee of the National Health Research and Development Program had recommended that the Blajchman–Feinman study be funded as long as the Red Cross did not implement surrogate and HCV testing. When the staff of the program learned that the Red Cross might implement one or more of these tests, Ms Lee, the director of research administration, wrote to Dr Perrault on 14 July 1989 asking "whether it is

still appropriate to consider this project, which depends on the availability of unscreened blood, for funding." Dr Hauser, the executive director of the Canadian Blood Committee, wrote on the same day to Dr Glynn, urging that the Department of National Health and Welfare fund the study whether or not HCV testing was implemented, and emphasizing that although "the cost of the project is high ... the cost of testing is almost 6 times the cost of this research project annually." Within a few days Dr Glynn agreed to recommend funding for the study provided that "periodic reviews are carried out on the progress of the study, and that agreement to carry out the study be communicated by the Health Protection Branch." On 20 July, Dr Boucher, who sat on the blood products review committee as a member, wrote to Ms Lee that "the Bureau of Biologics sees no objection to this proposed study to evaluate the use of surrogate markers ... As we do not know to what extent donor populations differ between countries, only a study in Canada will provide information relevant to the Canadian blood donor."

The deputy minister then recommended that the study be funded promptly, before the Red Cross implemented screening for non-A, non-B hepatitis. In a memorandum to the Minister dated 24 July 1989, she referred to the meeting between Dr Perrault and Dr Hauser on 7 July 1989, and said:

The CRCS [Canadian Red Cross Society] advised the CBC [Canadian Blood Committee] that for legal reasons, they would be recommending that Canadian Red Cross blood be screened, at an annual cost of almost \$17 million. The CRCS would be seeking funds for the screening through the CBC. From a scientific point of view it would be best to delay the decision to test until the results of Dr Feinman's study are available. Nevertheless the CRCS feels that the risk of successful litigation is too great to delay introduction of the testing.

Because the study might be ended if the Red Cross implemented testing, its public relations department recommended that funding be given without issuing a press release. Additional information was sent to the Minister in a memorandum from the deputy minister dated 31 July 1989, which referred to the serious clinical consequences of non-A, non-B hepatitis, the implementation of surrogate testing in other countries, and the plans of the Red Cross to implement anti-HCV testing. The memorandum said that "if surrogate testing is shown to be ineffective in preventing hepatitis the potential annual saving to Canada will be \$10 million," and that the Red Cross's legal advisers had recommended the introduction of surrogate testing. The recommendation that the study be funded did not end the matter, however, because the cost of the study would exceed \$1 million and therefore required the approval of the Treasury Board.

The investigators feared that further delay would jeopardize the study, and on 1 August Dr Feinman wrote to Dr Perrault that the implementation of HCV testing would not interfere with the conduct of the study. He also said that, based on a small number of patients in the pilot study, the investigators had observed a marked drop in the incidence of post-transfusion non-A, non-B hepatitis from 9.2 per cent in 1984 to less than 2 per cent in 1989. He attributed this drop to a better selection of donors and to the Red Cross's public education program, which encouraged persons at high risk of contracting AIDS to refrain voluntarily from donating blood.

In a letter to Dr Hauser dated 10 July 1989, Dr Perrault had suggested that funding for the Blajchman–Feinman study be addressed immediately and that a “blue-ribbon” committee of experts, including ethicists, be assembled to help resolve the issue of surrogate testing. He repeated this suggestion in a letter on 21 July to Dr Glynn. On 31 July, Dr Hauser sent a memorandum to members of the Canadian Blood Committee, reporting Dr Perrault's desire to “establish a committee to review the evidence and decide whether surrogate testing should be introduced prior to the completion of the [Blajchman–Feinman] study.” He said that the matter would be discussed at the next meeting of the committee. The suggestion was not pursued, however, and no mention of it is made in the minutes of subsequent meetings of the Canadian Blood Committee or the Red Cross.

By mid-August 1989 the National Health Research and Development Program had decided that the cost of the Blajchman–Feinman study was too high for it to support alone. It was suggested that the provinces, through the Canadian Blood Committee, share the cost. A special meeting by conference call of the Canadian Blood Committee was scheduled. In a background memorandum to committee members dated 16 August, Dr Hauser explained the importance of funding the study:

Up to now the justification for not implementing surrogate testing was that we were awaiting the results of this study. As a result of increasing liability concerns the legal counsel to the Red Cross have advised the organization to implement surrogate testing. A Non-A Non-B liability suit has already been launched against the Red Cross.

From an economic point of view (\$3.2 million expenditure for a possible \$10 million annual saving) the study is justified. From a scientific point of view it has considerable international importance as Canada is one of the few countries in the western world that have not introduced Non-A Non-B testing.

Bob Gamble [chair of the Canadian Blood Committee] would like to hold a telephone conference call in the near future to make a decision. The urgency

of this matter relates to the liability concerns as the study is the major justification for not introducing surrogate testing. Further delays increase the risk that future judgments could be made against the Red Cross.

In a postscript, Dr Hauser predicted that the test for HCV antibody would be licensed in January and said that, although the "current scientific evidence suggests that both the Chiron [HCV antibody] test and surrogate testing should be used to test for NonA NonB ... hopefully the Non-A Non-B research project will provide justification for not adding the surrogate tests."

The minutes of the conference call meeting, held on 22 August, record the following reasons for supporting the funding of the study:

... the project made economic sense. The two-year delay in finalizing the research project has delayed implementation of surrogate testing, potentially saving \$20 million. If the research project were not carried out the Red Cross would feel obliged to recommend the introduction of surrogate testing on the basis of current scientific evidence and the fact that all U.S. blood (and most European blood) is tested for Non-A, Non-B hepatitis. He pointed out that the worst case scenario was that the CBC [Canadian Blood Committee] would fund the research project at a cost of \$1.5 million and the project would show that Non-A Non-B testing is effective in preventing transmission. At this time the CBC would be obliged to introduce testing. Nevertheless, the findings of the research study will not be available for two years and if testing were introduced at this time an additional \$20 million would have been saved. The best case scenario is that for an expenditure of \$1.5 million surrogate testing would be shown not to be scientifically justified thereby saving \$10 million annually.

The committee agreed that the study should be funded.

On 29 August 1989, Dr Hauser wrote to Dr Perrault confirming that the Canadian Blood Committee would provide \$1.5 million for the study from the fractionation account. This was an account held by the Red Cross in trust for the provinces for expenditures related to factor concentrates. A "communications strategy" from the Health Services and Promotions Branch recommended that no publicity be given to the grant for the following reasons:

Publicizing the study, at this stage, could cause considerable public concern. It would highlight the fact that there is yet another disease transmitted through blood transfusions, for which Canada does not screen.

The public would also be made aware that screening for non-A, non-B hepatitis is being done in the United States and other countries and not in Canada. That could also cause concern. The Canadian Red Cross Society

concurs with this view. They feel an announcement would raise a number of questions for which the answers are very complex. A public debate on the safety of the blood system, at this time, would not be helpful.

By the time funding was approved, only 15 per cent of the total number of patients needed for the Blajchman–Feinman study had been recruited. More patients were needed in the study than had been expected because the incidence of post-transfusion non-A, non-B hepatitis was lower than expected, and this in turn increased the time required to complete the research. As it turned out, the final results were not available until the autumn of 1993 and were published in *The Lancet* in January 1995.

Testing for HCV antibody, August 1989–June 1990

By the end of the summer of 1989, direct testing for the presence of HCV antibody had been implemented in most countries of western Europe. Blood bankers believed that the test could eliminate as much as 80 per cent of non-A, non-B hepatitis. On 25 August, Dr Perrault told an internal Red Cross working group that he wanted to conduct training programs in the autumn so that the Red Cross would be ready to begin testing routinely as soon as the test was formally licensed by the U.S. Food and Drug Administration. The Health Protection Branch in Ottawa did not require the test kits to be licensed for use in Canada. Although the branch did license test kits to detect HIV, that was an exception. Ordinarily, manufacturers were required only to notify the branch of the availability of a test.

At a meeting of the Canadian Blood Committee held on 4–5 October, Dr Perrault said that he wanted to implement HCV-antibody testing as soon as it was approved. He also presented an estimated cost for testing, which, if approved, would become part of the national blood program and therefore an additional charge against the provinces. The committee agreed in principle to the implementation of HCV-antibody testing, but withheld final approval pending the submission of a detailed budget. Before receiving that final approval, Dr Perrault wrote to Dr Furesz, the director of the Bureau of Biologics, on 21 December and told him that the Red Cross was adding HCV-antibody testing to its standard operating procedures.

When the Canadian Blood Committee met again, on 13–14 December 1989, the need to justify the high cost of the study was raised. Dr Hauser said that approximately 4 per cent of persons receiving transfusions developed non-A, non-B hepatitis. Of these persons, 25 per cent would develop it in an acute form, and approximately 40 per cent of the patients infected would develop chronic hepatitis; the majority of those who developed chronic hepatitis would eventually develop cirrhosis or liver cancer or both. Dr Perrault

reported that the Red Cross had estimated the cost of a new case of non-A, non-B hepatitis to the health care system to be approximately \$700, including a "physician's visit, hepatic profile and liver biopsy." The minutes set out the following calculation of annual costs:

Calculations by Secretariat Based Upon the Above:

- 300,000 transfusion recipients x 4 per cent chance of a transfusion causing clinical NANB hepatitis = 12,000 potential patients with acute NANB infection
- 12,000 patients (less 1/3 who die of illness that required transfusion) x 40 per cent chance of developing chronic hepatitis = 3,200 potential patients with chronic hepatitis.

Therefore, the health care system will treat 12,000 cases of acute hepatitis at approx. \$700 = \$8.4 million.

It was recognized that many millions of dollars more a year would be required for hospital care and treatment for those patients who went on to develop chronic hepatitis, including those who developed cirrhosis and liver cancer. The committee formally approved the budget for HCV-antibody testing at a meeting on 1 May 1990. By that time, testing was well under way in most Red Cross blood centres.

Although the Red Cross originally thought that testing would begin early in 1990, it encountered difficulties in implementing HCV-antibody testing in several centres and delays in receiving equipment from suppliers. The majority of Red Cross centres began testing donations for HCV antibody in March, however, and testing was fully implemented throughout Canada by 30 June 1990.

Statistics compiled by the Canadian Red Cross between April and August 1990 showed that between 0.53 per cent and 0.8 per cent of blood donors were repeatedly reactive for HCV antibody, that is, they tested positive for the antibody in two successive tests. Predictably, the proportion of repeatedly reactive prospective donors declined as those who tested positive were removed from the donor pool. Dr Perrault told the Canadian Blood Committee that the proportion of donors identified as repeatedly reactive in Canada was similar to that in the United States. In an internal Red Cross memorandum, he observed that not all the donors so identified were believed to be HCV-antibody positive but that, because there was no confirmatory test, all had to be indefinitely deferred. A notice to blood donors was being posted at all clinics warning them of the possibility that they could be perfectly healthy even if they were deferred.

Consideration of surrogate testing, 1990

The introduction of HCV-antibody testing did not end the debate over surrogate tests, because uncertainty persisted about the efficacy of HCV-antibody testing in reducing the incidence of post-transfusion non-A, non-B hepatitis. Although early statistics suggested that a reduction of as much as 80 per cent could be achieved, data from later studies varied greatly and suggested a range of from 20 per cent to as high as 90 per cent. The HCV-antibody test proved to be reliable in detecting chronic cases of non-A, non-B hepatitis, but its efficacy was limited by a window period of eight weeks to one year, during which a person could be infected without developing symptoms or a detectable amount of antibody. Preliminary data indicated that only 3.9 per cent of donors found to have elevated ALT levels were identified as positive by HCV-antibody testing. Moreover, by the end of 1990, many researchers and blood bankers believed that non-A, non-B hepatitis was caused by at least one virus other than HCV, which might not be detected by the test for HCV antibody. There continued therefore to be some reason for conducting ALT and anti-HBc tests as surrogate tests for non-A, non-B hepatitis. In the United States, both surrogate tests were retained in order to identify infective units that might escape detection by HCV-antibody screening.

HCV-antibody testing had been incorporated into the Blajchman-Feinman study when the Red Cross implemented the test nationally. The investigators supported the continuing significance of the study in a letter to Dr Perrault in January 1990 in which they said:

It is very likely that with the introduction of the anti-HCV test, there will be a reduction in the occurrence of NANB post-transfusion hepatitis, however, the magnitude of this reduction at this time is unclear. From the available preliminary data, it appears that at least 50 per cent of the carriers of the hepatitis C virus (HCV) may not be identified with the new anti-HCV test. However, because of our current study, we will be in an excellent position to monitor the impact of anti-HCV testing and still ask the question as to whether surrogate testing is of some additional value in reducing the occurrence of NANB post-transfusion hepatitis.

They expressed the hope that within twelve months they would have preliminary data that would shed light on the efficacy of both HCV-antibody and surrogate testing.

Dr Blajchman presented an interim report at a meeting of the Red Cross medical directors on 25 October 1990. No specific numbers are recorded in the minutes, but the preliminary results were said to suggest that, except for units with very high ALT levels, surrogate tests were of questionable value.

Dr Blajchman told the medical directors that, because of the reduced incidence of post-transfusion non-A, non-B hepatitis, as many as 5,000 patients might be needed in order to complete the study. Dr Perrault repeated this information at a meeting of the Canadian Blood Committee advisory subcommittee four days later, and said that "the data collected to date supports the hypothesis that it is not necessary to screen blood using NANB surrogate tests."

Results of the Blajchman–Feinman multicentre study, 1993

The results of the Blajchman–Feinman multicentre study were announced on 2 September 1993 at a meeting organized by the Canadian Blood Agency, the successor to the Canadian Blood Committee. By that time, an improved, second generation of HCV-antibody tests had been introduced and less attention was being given to anti-HBc and ALT as surrogate tests for non-A, non-B hepatitis. Attention had shifted to the potential value of anti-HBc tests for reducing the incidence of post-transfusion hepatitis B by identifying carriers who would not be detected by other methods. The U.S. Food and Drug Administration had said in September 1991 that anti-HBc testing should be conducted for that purpose on all blood donations intended for transfusion. In June 1993, some twenty months later, the Bureau of Biologics in Ottawa let it be known that it would soon issue a decision about anti-HBc testing for hepatitis B in Canada. That prompted the Canadian Blood Agency decision to hold the meeting at which the Blajchman–Feinman results were reported.

The participants included Dr Blajchman and Dr Feinman, representatives of the Canadian Blood Agency, its scientific advisory committee, the Canadian Red Cross, and the Bureau of Biologics. Experts from the United States included Dr Alter of the National Institutes of Health and Dr James Mosley of the University of California at Los Angeles, one of the principal investigators of the TTV study. The purpose of the meeting was not to make decisions but to examine the most recent data and to consider whether the introduction of anti-HBc testing would reduce the incidence of post-transfusion hepatitis B or serve as a useful surrogate marker for hepatitis C, for non-A, non-B, non-C (NABC) hepatitis, or for HIV.

Although residual cases of post-transfusion hepatitis did occur, post-transfusion hepatitis B had not been a major problem for nearly twenty years. The data presented confirmed this. Dr Alter said that the "extremely low" estimates of transfusion-associated hepatitis B (0.5 per cent or less in recipients of transfusion) made it difficult to evaluate the role of anti-HBc testing in the prevention of hepatitis B. Dr Roger Dodd, of the American Red Cross, reported that, of 300 cases of post-transfusion hepatitis reported

to the American Red Cross in 1992, 100 were hepatitis B, and the rest were non-A, non-B hepatitis. Dr Blajchman and Dr Feinman reported that no cases of post-transfusion hepatitis B transmission were observed in their study.

Dr Alter also reported on the efficacy of testing in the United States. Before the introduction of surrogate testing, 4.5 per cent of patients developed post-transfusion hepatitis C (with a risk of 0.52 per cent per unit); after surrogate testing was introduced, those figures dropped to 3.4 per cent (0.36 per cent per unit); after the first-generation HCV-antibody test was introduced, they fell dramatically further – to 1.1 per cent (0.07 per cent per unit). The second generation of HCV-antibody testing had reduced the risk to less than 0.5 per cent per transfusion. Dr Alter said that, although “other factors such as donor selection and the introduction of anti-HIV [antibody] testing may have significantly altered the incidence of post-transfusion hepatitis C infection ... in retrospect it appears that anti-HBc testing unequivocally assisted in preventing hepatitis C and HIV infection in the time period prior to the availability of specific serological screening tests.”

The final data and conclusions of the Blajchman–Feinman study, although not yet published, confirmed what Dr Alter’s retrospective data suggested. The study demonstrated that surrogate testing had a substantial beneficial effect in reducing the incidence of post-transfusion non-A, non-B hepatitis before the introduction of HCV-antibody testing in 1990, but relatively little, if any, after that testing was implemented.

Before the Red Cross introduced HCV-antibody testing in 1990, the incidence of non-A, non-B post-transfusion hepatitis among the 392 participants in the study who received blood donations that had not been screened for either anti-HBc or ALT was 2.02 per cent (eight cases). Of these, five (1.26 per cent) were hepatitis C and 3 (0.76 per cent) were unidentified (non-A, non-B, non-C, or NABC) hepatitis. The incidence of post-transfusion non-A, non-B hepatitis among the 492 recipients of blood donations that had been screened for the surrogate markers was 0.5 per cent (two cases, both NABC hepatitis). They estimated that the benefit of surrogate testing for HCV before the introduction of HCV-antibody testing was 85 per cent. After HCV-antibody testing was implemented in 1990, the incidence of post-transfusion non-A, non-B hepatitis among the 1,880 patients who received blood unscreened by the surrogate tests declined to 0.86 per cent (sixteen cases). Of this group, five were hepatitis C (0.27 per cent) and eleven were NABC hepatitis (0.59 per cent). The corresponding data for the 1,909 who had received blood that had been screened with both surrogate tests were three (0.16 per cent) and ten (0.52 per cent), respectively. The difference in incidence among patients who received screened and unscreened donations, and accordingly the estimated benefit of surrogate testing for HCV, after the introduction of HCV-antibody testing was statistically insignificant. These results are summarized in Table 24.1.

Table 24.1
Post-transfusion hepatitis (PTH) rates before and after HCV testing

Screening of blood donations	Number of recipients	Cases of PTH		Cases of PTH			
		No.	%	with HCV		with NABC	
				No.	%	No.	%
<i>Before HCV screening was introduced</i>							
No surrogate screening	397	8	2.02	5	1.26	3	0.76
Surrogate screening	402	2	0.50	0	0	2	0.50
<i>After HCV screening was introduced</i>							
No surrogate screening	1,880	16	0.86	5	0.27	13	0.59
Surrogate screening	1,909	13	0.68	3	0.16	10	0.52

Based on: M.A. Blajchman et al., "Post-Transfusion Hepatitis: Impact of Non-A, Non-B Hepatitis Surrogate Tests," *The Lancet* 345 (7 January 1995):21-25. © by *The Lancet* 1995.

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The 9.2 per cent incidence of non-A, non-B hepatitis observed by Dr Feinman in 1983-5 fell to 2.02 per cent before the implementation of HCV-antibody testing, and fell to 0.86 per cent after the implementation of first-generation tests for the antibody to HCV. This decline occurred without the implementation of surrogate tests and was attributed to improved donor-screening methods.

The meeting concluded, on 3 September 1993, that

[i]t is clear that ongoing surveillance and improved mechanisms of reporting of transfusion-transmissible diseases is extremely important. The currently available assays for anti-HBc are associated with significant cost and continuing problems with specificity result as well as a substantial donor loss [sic], largely as a result of false positive reactions on screening. Fourteen of the twenty-one participants in this forum expressed opinions regarding the need for implementation of anti-HBc testing of the blood supply in Canada. Based on the evidence presented, there was a unanimous opinion that the introduction of anti-HBc testing would not significantly improve the safety of the Canadian blood supply with respect to the transmission of hepatitis B, hepatitis C, NABC hepatitis and HIV infection.

The representatives of the Bureau of Biologics and the Red Cross did not express an opinion. The invited experts from the United States and the members of the Canadian Blood Agency's scientific advisory committee who attended the meeting said that anti-HBc testing was unjustified. Neither surrogate test was ever implemented in Canada.

On 9–11 January 1995, the U.S. National Institutes of Health conducted a conference to consider whether surrogate testing of volunteer blood donations should be continued in the United States. The consensus statement developed at the conference recommended that ALT testing of volunteer blood donations be discontinued as it was no longer useful in detecting donors capable of transmitting hepatitis C. The consensus statement recommended, however, that anti-HBc testing of volunteer blood donations be continued. Although anti-HBc testing was no longer considered necessary as a surrogate for HCV, it was considered useful in identifying blood donors who might transmit either hepatitis B or HIV, but who were not detected by the specific tests for those viruses.

The Canadian Response to Post-Transfusion Hepatitis: Commentary

Unlike AIDS, hepatitis was known for decades to be transmissible by blood transfusion. Hepatitis was, however, widely accepted as an unfortunate but acceptable risk of blood transfusion and the use of blood products. This acceptance contributed to a lack of action, both in collecting data about the extent and seriousness of post-transfusion hepatitis and in taking measures to reduce its risk.

During the mid-1980s, a public debate took place in the United States about the use of surrogate tests to screen blood donations that might transmit non-A, non-B hepatitis. As a result of that debate, surrogate testing was adopted by U.S. blood-banking organizations in 1986. No comparable discussion occurred in Canada. In this country, there was no thorough assessment of the incidence of post-transfusion hepatitis in Canada, its seriousness, the efficacy of the surrogate tests, and the costs and benefits of their implementation. The discussion in Canada focused on costs and the fact that there had been no randomized study that would prove, rather than predict, the efficacy of the tests. At the same time, the public health consequences of the transmission of hepatitis to thousands of persons in Canada were not considered. The benefits of surrogate testing were not recognized in Canada until after the need for them had passed.

The extent of post-transfusion hepatitis in Canada

Hepatitis was known to be the most common, and – before the emergence of AIDS – the most serious, infectious disease transmitted through blood transfusion. The need for information about the extent and nature of post-transfusion hepatitis B was recognized in the early 1970s; the need for the same information about post-transfusion non-A, non-B hepatitis was recognized later in the decade. No reliable Canadian data were collected until the mid-1980s, when Dr Victor Feinman began a study of the incidence of post-transfusion non-A, non-B hepatitis in Toronto.

The inadequacy of the data available created an environment in which neither the Canadian Red Cross Society (Red Cross) nor provincial and federal health authorities felt it necessary to act to curb the spread of post-transfusion hepatitis in Canada. Canada was left without essential data throughout much of the debate on the value of ALT and anti-HBc as surrogate tests for non-A, non-B hepatitis.

The reporting of post-transfusion hepatitis

The most common method of obtaining data about the incidence of a disease is through physicians' reporting cases to the public health authorities. Because hepatitis's flu-like symptoms are frequently not recognized by physicians and may not develop in infected persons for many years, if at all, not all cases are reported. In 1971–2, the Red Cross began testing blood donations for the hepatitis B surface antigen (HBsAg), the presence of which indicates the donor is infected and is capable of transmitting the infection to others. However, the early tests detected only about 30 per cent of persons infected with hepatitis B. An analysis of test results published in 1973 suggested, moreover, that no more than one-quarter of the cases of post-transfusion hepatitis B were being reported. The Red Cross asked physicians, on several occasions in the early 1970s, to report cases of post-transfusion hepatitis to it; the Red Cross would then try to identify infected donors to ensure that they did not give blood again. Although the lack of reporting persisted, the Red Cross did not increase its appeals to physicians or begin programs to educate them about the nature and risk of post-transfusion hepatitis. Its efforts to improve reporting decreased after 1975, at a time when knowledge of non-A, non-B hepatitis was just beginning.

The issue of reporting post-transfusion hepatitis resurfaced in 1981 with the discussions about surrogate testing for non-A, non-B hepatitis. In its attempts to secure better data at this time, the Red Cross concentrated on developing a standard form to be used nationally for the reporting of cases of post-transfusion hepatitis. The hepatitis working group, an internal Red Cross committee, drafted a form for this purpose, but it was never adopted for national use.

The public health authorities too lacked information, despite provincial legislation requiring physicians to report cases of hepatitis. Public health officials took no measures to improve the reporting of hepatitis or to reinforce the Red Cross's requests for reports of post-transfusion hepatitis. Public health officials could have tried to educate physicians about the need for reporting either directly, or with the assistance of the colleges of physicians and surgeons. Nor did they always ask physicians, in the cases that were reported, about the source of infection, such as blood transfusion or the use of blood products. The data collected by provincial authorities about reported cases of hepatitis were tabulated nationally by the Laboratory Centre for Disease Control, but they were not classified according to the source of infection.

There was no coordination among provincial and federal public health agencies and the Red Cross of the collection of information about post-transfusion hepatitis or of ways to improve reporting.

Studies of post-transfusion hepatitis

In the United States, major studies had been conducted into the incidence of post-transfusion hepatitis and methods of reducing it since the 1950s; by the mid-1970s, U.S. studies were investigating the nature of non-A, non-B hepatitis. In Canada, the first major study of post-transfusion hepatitis was not begun until 1984.

The Red Cross recognized the need for such a study beginning in 1973. In April 1975, the Red Cross's national scientific advisory committee (the predecessor of the blood transfusion service advisory committee) discussed the need for better information about the incidence of post-transfusion hepatitis in Canada. The members of the committee hoped at that time that other organizations with an interest in post-transfusion hepatitis might devise a surveillance program with the Red Cross. The Red Cross had no specific budget for research until 1983. Even then, the cost of a major study would likely have consumed most, if not all, of its research budget for several years. To undertake the work themselves or in association with others, researchers in the Red Cross would have had to seek financial assistance from granting agencies. They did not do so until late 1987, when Dr Morris Blajchman, the medical director of the Red Cross's blood centre in Hamilton and a professor in the faculty of medicine at McMaster University, applied for funding for a multicentre study of the efficacy of surrogate testing in Canada. Research on post-transfusion hepatitis was recognized as a subject worthy of study when the applications for funds by Dr Feinman in 1983 and by Dr Feinman and Dr Blajchman in 1987 were approved and the necessary funds were granted.

When the possibility of using surrogate testing for non-A, non-B hepatitis arose in 1981, the Red Cross's blood transfusion service advisory committee decided that no action should be taken until there were Canadian data to justify making a decision. It did not, however, recommend that the Red Cross take steps to collect the necessary data. The Laboratory Centre for Disease Control, which was represented on the committee, also took no steps to collect the data. The significance of the discussions about ALT testing at this time lay less in the decision not to implement ALT testing than in the missed opportunity to study the incidence of post-transfusion hepatitis and the efficacy of surrogate testing in Canada.

Estimating the risk of post-transfusion non-A, non-B hepatitis

The only information available to the blood transfusion service advisory committee in 1981 about the incidence of post-transfusion non-A, non-B hepatitis in Canada was the number of cases reported to the Red Cross. It was known that only a small fraction of the cases of post-transfusion hepatitis were reported.

The incidence of the disease in the United States, which had been examined in various studies, could have served as a basis for estimating the Canadian incidence, but neither the Red Cross nor the Laboratory Centre for Disease Control made use of it. The analysis of test results at the Toronto blood centre published in 1973 had found that 0.15 per cent of the donations tested positive for the hepatitis B surface antigen, a proportion consistent with U.S. data. Given these data and the epidemiological similarities between non-A, non-B hepatitis and hepatitis B, it would have been prudent to assume that the incidence of post-transfusion non-A, non-B hepatitis in Canada, at least in urban areas, was comparable to that associated with volunteer donors in the United States, which was as high as 10 per cent in certain regions. Dr Feinman's Toronto incidence study later confirmed that this assumption was correct. His study showed the incidence of post-transfusion non-A, non-B hepatitis in Toronto to be 9.2 per cent.

The Red Cross and others thought that the incidence in Canada would be substantially lower than that in the United States because Canada relied almost entirely on volunteer donations of whole blood. Although this distinction could be made as it pertained to the use of plasma from paid donors in the manufacture of blood products, blood components for transfusion in the United States were obtained almost entirely from volunteer donations. Nevertheless, it was commonly believed that the Canadian blood system was safer than that of the United States. However, volunteer donors were associated with infections of non-A, non-B hepatitis in as many as 10 per cent of the recipients of transfusions in certain parts of the United States. These data were known to the Red Cross by 1978 and hepatitis was known to be a common risk of blood transfusion in Canada.

Reducing the risk of post-transfusion hepatitis

Donor screening

As discussed in Chapter 22, asking prospective blood donors questions about their health or behaviour continued to be an important method used by the Red Cross to defer donors at risk of transmitting hepatitis after hepatitis B testing was introduced in 1971–2. Even so, questioning was of limited effectiveness in screening out donors with non-A, non-B hepatitis because infected persons can remain symptom-free for as many as twenty years.

The Red Cross permanently deferred prospective donors who said that they had a history of hepatitis or jaundice and temporarily deferred those who said they had been exposed to a person with hepatitis. The questions prospective blood donors were asked were not expanded to include references to the groups at high risk of contracting AIDS until well after the introduction of HIV-antibody testing. There had previously been no questions designed to identify and to defer prospective donors who belonged to any of these high-risk groups, although it had been known since the 1970s that some of them,

in particular homosexual men and intravenous drug users, had a higher than average risk of contracting hepatitis. Because of the lengthy latency period during which persons with hepatitis exhibited no symptoms, these questions, and in particular questions about intravenous drug use, would have screened out donors at risk for non-A, non-B hepatitis more effectively than the general hepatitis questions that were asked.

Donor deferral

When a person was diagnosed with hepatitis that had apparently been transmitted through a blood component, the Red Cross could often identify the donor or donors whose blood had been used. The process was laborious and time-consuming if the patient had received many blood components. The Red Cross's hepatitis working group recommended in July 1981 that all donors implicated in a case of post-transfusion hepatitis be tested for the presence of the hepatitis B surface antigen or, if non-A, non-B hepatitis was suspected, for elevated levels of alanine amino transferase (ALT). The working group's recommendation was rejected by the medical directors of the Red Cross's blood centres, who decided that the exclusion of implicated donors should be at the discretion of the local medical director. In the absence of a requirement to defer implicated donors, many donors who transmitted hepatitis would unknowingly continue to donate blood.

The consideration of surrogate testing

The most effective method of identifying blood donors who carry infectious diseases is to test all blood donations. Before the development of the HCV-antibody test, two kinds of surrogate tests were considered for screening donated blood for what was then called non-A, non-B hepatitis. One measured the level of alanine amino transferase (ALT) in a donor's blood; the other detected the antibody to the hepatitis B core antigen (anti-HBc). These tests, and their use as surrogate tests for non-A, non-B hepatitis, are described in Chapter 23.

Surrogate tests are usually less effective than specific tests, and frequently result in the rejection of many blood donors who are in fact not infected and donations that are not contaminated. In deciding whether to implement a surrogate test, several factors must be considered, including the incidence of the disease among the recipients of transfusions, alternative measures to reduce the incidence, the seriousness of the disease, the cost of the testing, and the number of donors who will be rejected as a result of the testing.

The incidence of post-transfusion hepatitis

Whether resources should be devoted to any screening test depends in part on the number of persons at risk. The expense may be difficult to justify if the incidence of a post-transfusion infection or the effectiveness of the test is low.

If the incidence is high, the implementation of testing may be justified even if the test can detect as few as 30 per cent of infected donations, as was the case when testing for the hepatitis B surface antigen began in 1971–2.

The results of two major U.S. research projects to study surrogate testing for non-A, non-B hepatitis, the transfusion transmitted viruses (TTV) study and the National Institutes of Health (NIH) study, showed that the use of ALT and anti-HBc testing of blood donations could reduce the incidence of post-transfusion non-A, non-B hepatitis by 60 per cent. Surrogate testing was adopted in the United States in 1986 in large part on the basis of these studies. In addition, the incidence of post-transfusion non-A, non-B hepatitis in that country was significant and the understanding of the seriousness of the disease in that country had grown.

The Red Cross was aware that a decision to implement surrogate testing in the United States would put pressure on it to do the same in Canada. In January 1986, Dr Roger Perrault, the national director of the blood transfusion service, wrote to Dr Denise Leclerc-Chevalier, the executive director of the Canadian Blood Committee, and said that the Red Cross would look carefully at the results of Dr Feinman's study in Toronto and that it would be "very important to see if there is any difference between Canadian and American data in this regard, as the implementation of another screening test (in addition to HIV testing) would mean a significant expenditure to the CRCS [Canadian Red Cross Society] blood program." By this date, however, the preliminary data from the Toronto incidence study had already suggested that the incidence of post-transfusion non-A, non-B hepatitis was 7.6 per cent, within what was believed to be the U.S. range.

After the decision to implement surrogate testing was made in the United States, the Red Cross began to question the design of, and the data from, Dr Feinman's study. The Red Cross had discussed the design with Dr Feinman in 1984 and had decided that, given his work, it would not proceed with an incidence study of its own. If the Red Cross had not been satisfied that the Toronto incidence study would provide accurate data, it could have proceeded with an incidence study of its own. In 1986, the Red Cross criticized the Toronto incidence study, rather than accept its evidence that the incidence of post-transfusion non-A, non-B hepatitis was as great in Canada as in parts of the United States.

Blood bankers in the United States accepted the data from the Toronto incidence study. After the final results of the study became known, several American blood bankers expressed support for a multicentre study of the efficacy of surrogate testing in Canada because the Toronto study had shown the incidence of post-transfusion hepatitis in Toronto to be similar to that observed in many parts of the United States. Rather than criticize the data from the Toronto incidence study, it would have been reasonable for the Red Cross to accept it as evidence of a significant problem, and to act swiftly to find ways to reduce it.

HIV-antibody testing as a surrogate test for non-A, non-B hepatitis

The Red Cross also questioned the validity of the results of the Toronto incidence study because it was conducted between 1983 and 1985, before blood donations were screened for HIV antibody. The Red Cross hoped that HIV-antibody testing could in itself be an effective surrogate test for non-A, non-B hepatitis because of the epidemiological similarities between the two diseases, in particular the similarities in modes of transmission and high-risk groups. However, the prevalence of HIV among Canadian blood donors was much lower than the prevalence of non-A, non-B hepatitis. The use of HIV-antibody testing as a surrogate test for non-A, non-B hepatitis would therefore identify only a small proportion of the donors who might transmit non-A, non-B hepatitis.

The Red Cross relied on HIV-antibody testing, which had already been implemented, as a surrogate for non-A, non-B hepatitis at the same time that it rejected anti-HBc as a surrogate for non-A, non-B hepatitis. Yet, the evidence of the efficacy of ALT and anti-HBc testing as surrogates for non-A, non-B hepatitis was strong. Evidence of the efficacy of HIV-antibody testing as a surrogate for non-A, non-B hepatitis was non-existent. In its submission, the Red Cross acknowledged that there were no studies that showed HIV-antibody testing to be an effective surrogate test for non-A, non-B hepatitis. But, it added, this was "a view that was widely held by numerous transfusion experts." However, HIV-antibody testing had been implemented in the United States nearly a year before the U.S. Food and Drug Administration's blood products advisory committee recommended that surrogate testing be implemented. Moreover, that committee made its recommendation after considering the limited extent to which HIV-antibody testing would act as a surrogate for non-A, non-B hepatitis.

The hypothesis that testing for the HIV antibody would reduce the incidence of non-A, non-B hepatitis could have been tested without great difficulty or expense. In March 1985, the medical director of the Calgary blood centre wrote to Dr Perrault asking whether Dr Feinman's incidence study "could be continued to see if there is a decreased incidence after the introduction of AIDS associated virus testing." Dr Martin Davey, the assistant national director of the blood transfusion service, who replied on behalf of Dr Perrault on 15 April 1985, stated that Dr Feinman was "not open to requests to change his plans." In fact, Dr Feinman was never asked to do so. The suggestion was not pursued. The Toronto incidence study stopped collecting data on 30 October 1985, two days before the Red Cross completed its implementation of HIV-antibody testing nationally.

Dr Perrault also suggested to the Red Cross's blood transfusion service advisory committee that the confidential unit exclusion program, which allowed donors to indicate confidentially that their blood should not be used for transfusion, would screen donors at increased risk of transmitting non-A,

non-B hepatitis. A study of the program at the Toronto blood centre was published in *Transfusion* in 1987. It found that 7.5 per cent of the donors who indicated that their blood should be used only for laboratory purposes were anti-HBc positive, compared with 0.8 per cent of a control group. However, fewer than 1 per cent of all donors had designated that their blood should not be used for transfusion. Confidential unit exclusion could not therefore be expected to approach the 60 per cent reduction in incidence predicted for combined surrogate testing. The program, moreover, was not implemented nationally until the autumn of 1988.

The clinical consequences of non-A, non-B hepatitis

A virus may be widespread but not cause serious illness in everyone infected. Cytomegalovirus, for example, is highly prevalent in the Canadian population and among blood donors, but in most cases does not cause adverse effects. Both the Red Cross and the Government of Canada submitted that the decision not to implement surrogate testing in Canada resulted in part from a failure to appreciate the serious clinical consequences of non-A, non-B hepatitis. In its submission, the Red Cross said that until the mid- to late-1980s non-A, non-B hepatitis was commonly believed to be a relatively mild disease, which "although undesirable ... was viewed as a tolerable transfusion related risk." By 1980, some studies had shown that between 25 and 50 per cent of persons infected with non-A, non-B hepatitis had prolonged abnormal levels of ALT, and that of this group the majority showed evidence of chronic active hepatitis and 10 to 12 per cent showed evidence of cirrhosis. However, little attention was given to the data demonstrating the serious consequences of non-A, non-B hepatitis until 1984, when a study at the U.S. National Institutes of Health found that as many as 20 per cent of patients with chronic non-A, non-B hepatitis developed cirrhosis. By the mid-1980s, non-A, non-B hepatitis was known to cause serious disease, including cirrhosis and liver cancer, in a significant proportion of infected individuals. The seriousness of non-A, non-B hepatitis was one of the reasons that surrogate testing was implemented in the United States.

The Red Cross sent representatives to a symposium at the American Red Cross in 1984 at which data on the serious clinical consequences of non-A, non-B hepatitis were presented. This information appeared in various documents and position papers prepared by Red Cross employees about post-transfusion hepatitis and surrogate testing. There was little discussion, however, about the implications of this information. Dr Feinman and his colleagues calculated that, based on an incidence of 9.2 per cent among recipients of transfusions, 4,048 persons would have contracted non-A, non-B hepatitis in Toronto from blood components during 1984, and of these 1,457 would progress to chronic hepatitis. They said that the number that would eventually develop cirrhosis or liver cancer was unknown. In 1984, however, it was believed that 10 per cent of those with chronic hepatitis would do so.

The costs of surrogate testing

The Canadian Blood Committee and the Red Cross were understandably concerned about the cost of implementing the combined surrogate tests for non-A, non-B hepatitis. The Red Cross's estimates of the cost varied from \$5 million to almost \$20 million per year, depending on what was included in the total. Even the lower estimate must have seemed high if, as argued, the tests would prevent only a small number of cases of a disease that had no serious clinical consequences.

A cost-benefit analysis of ALT testing, published in the *New England Journal of Medicine* in 1982, showed that "the decision to undertake the ALT testing program would return more in benefits to society than the costs required to implement the program." It weighed the costs of surrogate testing, including the direct cost of the tests, the loss of donors, and the cost of the consequent increased efforts in donor recruitment, against the benefits, which were defined as the "expected costs of hepatitis potentially avoided." The financial benefit of ALT testing was estimated to be either \$8,018 or \$13,142 per 1,000 units of blood, depending on which of the NIH and TTV studies was used as the source of data. Another study, published in the *Journal of the American Medical Association* in 1984, used a different method of calculation but also concluded that an investment in ALT testing would return a net benefit, estimated to be \$741.76 per case of post-transfusion non-A, non-B hepatitis prevented.

The Red Cross was convinced that the cost of surrogate testing outweighed its benefits. However, a proper cost-benefit analysis of the implementation of ALT or anti-HBc testing was never performed in Canada. On one occasion in 1986, when the Red Cross tried to estimate the broader social costs of implementing surrogate testing, it did not take into account the medical and social costs of post-transfusion non-A, non-B hepatitis and therefore the savings that might be achieved through testing. In the absence of a cost-benefit analysis of surrogate testing in Canada, there was no reasonable basis for a belief that the costs of surrogate testing outweighed its benefits.

The loss of donors

Surrogate testing would have led to the deferral of a significant number of donors, many of whom would have been deferred unnecessarily. When in 1986 the Red Cross estimated the costs of surrogate testing, it assumed that 5 per cent of donors would be deferred. That proportion was similar to that expected in the United States, although it was far lower than was expected in countries such as Spain and Italy. A loss of 5 per cent might not be a serious matter for blood programs that collected more blood than was needed, but the Red Cross had experienced serious blood shortages during the 1980s, particularly in Toronto, Vancouver, and Montreal. In his testimony, Dr Perrault described the "erosion of the donor base" as one of the "key realities" of the time. There was also a lot of concern that recognition, through testing, of

another transfusion-transmitted disease, especially one that had been known for more than a decade, might permanently destroy the confidence of the public, especially blood donors, in its work.

Although it was essential that the Red Cross be able to provide an adequate supply of blood components for transfusion, a threat of shortage was not more important than a threat to the safety of the blood that was collected and transfused. The appropriate response to blood shortages is increased education about the proper use of blood components and blood products and improvements in the recruitment of blood donors.

The rejection of surrogate testing in Canada

The Red Cross's internal committees that decided to reject surrogate testing lacked both the expertise and the information necessary for appropriate decisions. In the end, surrogate testing was rejected in favour of a multi-centre study, which was beset by delays. The study demonstrated that surrogate testing would have been effective in reducing post-transfusion non-A, non-B hepatitis, had it been introduced before the implementation of a specific test for hepatitis C.

The Red Cross's decision-making process

In the United States, the issue of surrogate testing was considered in great detail by several committees composed of representatives of the major blood-banking organizations, interested government agencies, and experts in post-transfusion hepatitis. In making their decisions, they had the benefit of two major research projects, one funded by the National Heart, Lung, and Blood Institute (the TTV study), the other conducted by the National Institutes of Health (the NIH study). In Canada, a conference of experts to consider the implementation of surrogate testing was not convened until September 1993, three years after HCV-antibody testing had been implemented in Canada.

As the operator of the national blood program, the Red Cross was the protector of Canada's blood supply and was deferred to by physicians and government officials for its expertise. Its tasks included deciding whether surrogate testing for non-A, non-B hepatitis should be implemented. The Red Cross made its decisions with respect to transfusion-transmitted non-A, non-B hepatitis through committees that lacked necessary information and expertise, and without involving the group most expert in the subject, the hepatitis working group. The result was a decision that was premised on inaccurate information about, and poor assessments of, the nature and extent of post-transfusion non-A, non-B hepatitis in Canada, the efficacy of surrogate testing, and developments in other parts of the world.

The issue of surrogate testing of blood donations was discussed at meetings of the blood transfusion service advisory committee and of the medical

directors, but only as one of many items on the agenda. It was never given detailed consideration. Although some members of both committees were knowledgeable about blood transfusion and, to some extent, post-transfusion hepatitis, the committees relied on information and advice from members of the national office of the blood transfusion service. The Red Cross's board of directors, which gave final approval to decisions about safety, was composed mainly of lay persons and depended on the advice given to it by the advisory committee and the national office of the blood transfusion service. The committees invariably followed the recommendations of the national office, which was predisposed against surrogate testing. Expressions of support for surrogate testing within the Red Cross were rare. When other views were expressed, they were not always heeded, even when they came from those most knowledgeable about hepatitis.

The one committee of the Red Cross that was concerned specifically with issues related to post-transfusion hepatitis, the hepatitis working group, was not involved in making the decision. Its terms of reference expressly included post-transfusion hepatitis, and it had been given a "watching brief" for the subject by the blood transfusion service advisory committee in 1981. Yet it considered surrogate testing on only one occasion – in 1985, when the discussion was confined to the question whether the Red Cross should require ALT testing of plasma intended for fractionation. The hepatitis working group did not evaluate all the information available in deciding to continue to accept plasma products untested for ALT levels. In 1986 the hepatitis working group was absorbed into a new group, the transmissible diseases and immunology working group, which at the time was preoccupied with issues related to AIDS and HIV-antibody testing. Neither this new working group, nor any other committee of the Red Cross, reconsidered the decision of the hepatitis working group after the Red Cross learned that the American fractionators had begun to use only plasma tested for ALT levels.

The events in the United States

The decision not to implement surrogate testing in Canada was influenced by the Red Cross's interpretation of events in the United States, and in particular the data from the TTV and NIH studies. Position papers prepared by employees of the national office of the blood transfusion service, for distribution at meetings of committees of the Red Cross and of the Canadian Blood Committee, contained inaccurate statements. These inaccuracies included the statement that surrogate testing in the United States was "experimental" and the statement that some major participants in the U.S. blood system had rejected surrogate testing. These statements minimized the significance of the decision in the United States, and the data on which it was based. Surrogate testing was not at that time experimental in the United States. A policy decision had been reached on the basis of two major studies

after the limitations of the data and the advantages and disadvantages of surrogate testing had been fully discussed by blood bankers and experts in post-transfusion hepatitis.

To the Red Cross the TTV and NIH studies did not demonstrate conclusively that surrogate testing was effective. The potential reduction of 60 per cent in the incidence of non-A, non-B hepatitis was not mentioned in any position paper prepared by the Red Cross for the Canadian Blood Committee. The position papers prepared for the various committees also implied that Dr Feinman's study of the incidence of post-transfusion hepatitis in Toronto would examine the efficacy of ALT testing, and suggested that any decision should await the results of that study.

The multicentre study on the efficacy of surrogate testing

Although the multicentre, randomized, controlled study of the efficacy of surrogate tests in reducing post-transfusion non-A, non-B hepatitis produced useful information, the need for such a study had passed before it was begun. By the mid-1980s, the significance of the incidence of post-transfusion non-A, non-B hepatitis and its serious clinical consequences should have been appreciated. These facts were recognized in the United States, where the debate over implementing surrogate testing had been resolved on the strength of the existing data in 1986.

The support of the Canadian Blood Committee's advisory subcommittee for the multicentre study in October 1987 depended, at least in part, on the Red Cross's estimate that preliminary results from the study would be available in one year. Even before the delays in approval and funding, this estimate was optimistic. The acting national director of the blood transfusion service told the advisory subcommittee that, if funding were not available to conduct the study within one year, the Red Cross should proceed to implement surrogate testing. The advisory subcommittee in turn recommended that, if the multicentre study were not feasible within a reasonable time, the possibility of implementing surrogate testing should be considered. A year and a half later, funding for the study had not yet received final approval, and the study was not expected to be completed until 1991. Nevertheless, the possibility of implementing surrogate testing was not considered. By that time the Red Cross had convinced the Canadian Blood Committee not only that the study was needed but that it was an inexpensive alternative to surrogate testing.

The role of the Bureau of Biologics

The Bureau of Biologics' regulatory authority over the blood system was limited to the drugs listed in Schedule D to the *Food and Drugs Act*. "Human plasma collected by plasmapheresis," called source plasma, was added to Schedule D in 1978. However, most of the plasma collected in Canada was recovered from donations of whole blood. The collection of whole blood

and the separation and processing of its components, including recovered plasma, was not regulated by the Bureau of Biologics until "blood" was added to Schedule D in 1989. The scope of the bureau's regulatory authority is set out in greater detail in Chapter 6.

As discussed in that chapter, the bureau's authority to regulate the safety of "preparations from human sources," including factor concentrates, gave it indirect authority over the whole-blood donations collected by the Red Cross throughout the 1980s, and from which more than 90 per cent of the Canadian plasma used to manufacture blood products was recovered. The Bureau of Biologics could have required manufacturers of blood products to use only plasma tested with one or both of the surrogate tests for non-A, non-B hepatitis. To meet this requirement, the manufacturers would in turn have required their plasma suppliers to satisfy them that they had implemented these procedures. The Red Cross would have had to conduct surrogate testing of all the plasma it intended to have custom fractionated in order to meet this requirement.

Participation in decision making about surrogate testing

The bureau and the Red Cross first discussed using ALT levels as a surrogate test for non-A, non-B hepatitis at a meeting in July 1981. At that time, it was decided that further study was necessary before a decision could be made. Dr John Furesz, the director of the bureau, expected that the Red Cross would let the bureau know of any developments in ALT testing. However, the bureau was not informed when the blood transfusion service decided in November 1981 that ALT testing was inappropriate at that time.

The crucial discussions about surrogate testing occurred principally at meetings of various internal committees of the Red Cross, in particular its blood transfusion service advisory committee and medical directors' committee, and at meetings of the Canadian Blood Committee and its advisory subcommittee. The discussions at these meetings related to surrogate testing of all blood collected by the Red Cross in Canada, not merely to surrogate testing of the plasma used to manufacture the blood products. Representatives of the Bureau of Biologics regularly attended these meetings and did not limit their participation to discussions of blood products. The Government of Canada said in its submission that although "it was not necessary for the BoB [Bureau of Biologics] to take a formal position [on surrogate testing of whole-blood donations] ... it supported the assessment of the BTS [blood transfusion service] members."

Consideration of anti-HBc testing of plasma to be used in the manufacture of blood products

The first record of an internal discussion of surrogate testing in the bureau was an exchange of memoranda between Dr Furesz and Dr Wark Boucher, the chief of the bureau's blood products division, in November 1987. The

memoranda dealt with the adverse consequences of using anti-HBc testing to reduce the incidence of non-A, non-B hepatitis. Units of blood or plasma that contained antibodies to the hepatitis B core antigen (anti-HBc) were also likely to contain the antibodies to the hepatitis B surface antigen (anti-HBs), the antibodies that neutralize the virus and protect the body against future infection with the same disease. As explained in Chapter 24, the protective effect of anti-HBs was understood to occur even when many units of plasma were pooled together before being manufactured into blood products. The protective effect of anti-HBs was thus believed to reduce the infectivity of any units in the pool that were hepatitis B positive and had escaped detection by regular testing. In addition, some blood products, such as immune globulins, require a certain level of anti-HBs to be effective. Because anti-HBc and anti-HBs exist in the bloodstream at approximately the same time, removing donations containing one removes the other. For this reason, Dr Boucher described anti-HBc testing as a hazard in a memorandum to Dr Furesz and told the Canadian Blood Committee that "blood lacking HB core antibody may be more hazardous than blood containing it ... unless the valuable hepatitis B antibodies could be maintained in the plasma pool."

Dr Boucher's comments applied only to fractionated blood products, which are manufactured from the pooled plasma of thousands of donors, and not to blood components used in transfusions. Dr Boucher did not make this distinction clear to the members of the committee, however. Although the executive director of the Canadian Blood Committee would have understood that there was a distinction, most members were on the committee because of their understanding of financial matters within their respective departments or ministries.

When the blood products advisory committee of the U.S. Food and Drug Administration recommended that both ALT and anti-HBc be implemented as surrogate tests for non-A, non-B hepatitis, it limited its recommendation to donations of whole blood, excluding plasma collected by plasmapheresis. It did so to ensure a supply of plasma that was anti-HBs positive for fractionation into blood products, including immune globulin preparations. The United States had no difficulty in making a distinction in testing between donations of whole blood and plasma collected by plasmapheresis because its blood collection system was different from Canada's. In the United States, only approximately 25 per cent of the plasma used to manufacture blood products was recovered from whole-blood donations; the rest was collected by plasmapheresis. It was possible therefore to test whole-blood donations for anti-HBc without seriously reducing the number of units of plasma destined for fractionation. In Canada, most of the plasma collected for manufacture into blood products was recovered from whole-blood donations. To remove all units of blood that were anti-HBc positive could result in the consequences described by Dr Boucher. The Bureau of Biologics thus was

restricted in its ability to make a decision about anti-HBc testing by considerations of safety as well as by its lack of authority to regulate the collection of whole blood.

Consideration of ALT testing of plasma to be used in the manufacture of blood products

The potential hazards of anti-HBc testing of plasma for fractionation did not apply to using ALT as a surrogate test for non-A, non-B hepatitis. The blood products advisory committee of the U.S. Food and Drug Administration had not drawn a distinction between the two tests in its first recommendation. One year later, however, that committee recommended that all plasma, including that collected by plasmapheresis, be tested for ALT levels. The distinction between anti-HBc and ALT testing was not discussed at any of the meetings of the Red Cross or the Canadian Blood Committee.

In 1985, the German regulatory authorities required blood products used in that country to be prepared from plasma tested and found to have ALT levels lower than twice the upper limit of normal. To meet the German requirement, some U.S. manufacturers began to test a portion of their plasma for ALT levels. Plasma that met the German standard was manufactured by U.S. manufacturers into products for export to that country; the rest of the plasma that was tested – so long as the ALT level was no greater than five times the upper limit of normal – was made into products for sale elsewhere. The U.S. Food and Drug Administration and the National Hemophilia Foundation were troubled by the fact that factor concentrates manufactured in the United States for export to Germany were safer than those available domestically. If a substantial portion of the safest plasma was being made into products for export, the average level of ALT in the remaining plasma was increased. The German requirement had the potential to affect the quality of the factor concentrate manufactured in the United States that was being imported into Canada. Dr Furesz, the director of the bureau, testified that he was unaware of the German regulatory requirement at the time. He testified that, although he expected the Red Cross to keep the bureau informed of such matters, it did not do so in this case.

As early as August 1984, the bureau was made aware through an application to distribute its products in Canada that at least one manufacturer was using plasma tested for ALT levels. By the end of 1987, all plasma intended for fractionation was routinely being tested for ALT levels in the United States. The Bureau of Biologics did not discuss the addition of ALT testing with the manufacturers. Nor, despite the growing trend towards ALT testing in the United States, did it question the Red Cross's policy to distribute blood products manufactured from Canadian plasma that had not been tested for ALT levels, and that did not therefore meet the U.S. standard for the industry.

The bureau did not discuss whether the Red Cross should require ALT testing of plasma used for fractionation until November 1987. Even then, the discussion was informal, did not involve a full examination of the relevant information, and was marginal to an exchange of memoranda about the disposition of certain lots of factor concentrate that had been implicated in the transmission of hepatitis B or non-A, non-B hepatitis. Dr Boucher recommended ALT testing with increasing emphasis in three memoranda to Dr Furesz. He first wrote: "Obviously, if we did ALT screening we could at least state that we were at a level of testing (albeit questionable) of the US, UK, Germany, France, etc.," which was followed by, "In my opinion, ALT testing is questionable but harmless. There is a marginal benefit ... " Finally, he said: "I think that we should allow these [suspect] pools to be used and that we should require or strongly recommend that [the Red Cross] start ALT testing." His recommendation was not followed. In his testimony, Dr Furesz said that the reason he had not pursued it further was most likely that he "did not think really that we would accomplish anything by doing that."

A serious consideration of Dr Boucher's recommendation would have included a careful examination of information about the regulations of Germany and other countries, the recommendations of the U.S. Food and Drug Administration's blood products advisory committee, the practices of the U.S. manufacturers, the extent and seriousness of non-A, non-B hepatitis among users of factor concentrates, and the scientific data about the efficacy of ALT testing as a surrogate for non-A, non-B hepatitis. The bureau relied on the Red Cross for this information. For example, no representative from the bureau attended the meeting of the U.S. Food and Drug Administration's blood products advisory committee in February 1986, and the bureau did not consult any of the experts who made presentations at that meeting. Dr Furesz testified that he had relied instead on the information given to him by the experts at a meeting of the Red Cross's blood transfusion service advisory committee in April 1986. None of the members of that advisory committee was an expert in the subjects of hepatitis and surrogate testing. The committee relied on information in a position paper prepared by the national office of the blood transfusion service, which was incomplete and inaccurate in some of its statements. By relying so heavily on the information and expertise of the Red Cross, the Bureau of Biologics in effect made itself dependent upon the very organization whose activities it was supposed to regulate.

The Canadian Blood Committee

Although funding was always one of the Canadian Blood Committee's principal functions, its original terms of reference included the direction of the blood program, in accordance with the principles established by the provincial ministers of health; the establishment of policies; and the development and monitoring of standards. Very quickly, however, its attention became narrowly focused on issues of funding.

With respect to surrogate testing for non-A, non-B hepatitis, its interest from the outset was the direct cost of implementation. The committee's preoccupation with cost was well known to the Red Cross, which reported to it that the cost of testing could be as high as \$20 million in the first year. In early 1988, the Red Cross stated that unless the multicentre study was funded the Red Cross would have no choice but to implement surrogate testing. The committee's acceptance of the Red Cross's proposal – to study the efficacy of the surrogate tests rather than implement them – was seen as the least expensive course of action in the short term. The committee finally agreed to help support the study financially because "it made economic sense" and the "two-year delay in finalizing the research project has delayed implementation of surrogate testing, potentially saving \$20 million," with a potential for further savings until the results of the study became available.

The committee's advisory subcommittee supported the proposal for the multicentre study in October 1987 after it had been told that preliminary test results would be available in a year. It recommended that, if the study could not be done within a reasonable period, consideration should be given to the implementation of surrogate testing. When the study was delayed, neither the committee nor its advisory subcommittee revisited the question of implementation.

The committee never asked its advisory subcommittee for an independent assessment of the need for surrogate testing in Canada. The subcommittee existed to give the Canadian Blood Committee the expert advice it needed to make informed decisions. Its members, however, were chosen as representatives of organizations interested in the blood system rather than for any specific competence in the science or practice of blood transfusion. At the time the subcommittee was formed, it was expected that it would establish expert working groups or task forces to examine specific issues. No such expert group was established to evaluate surrogate testing. Although Dr Irwin Walker, a hemophilia treater who was a member of the advisory subcommittee, proposed that the subcommittee establish such a working group, his proposal was never placed before the Canadian Blood Committee for consideration. When Dr Perrault suggested in 1989 that an expert committee be formed to decide whether surrogate testing should be implemented before the multicentre study was completed, the committee again took no action on the matter. Although the Canadian Blood Committee's successor, the Canadian Blood Agency, held a meeting of experts to consider surrogate testing, the meeting did not take place until September 1993, three years after HCV-antibody testing had been implemented.

In the absence of an expert working group, the committee and its advisory subcommittee deferred to Dr Perrault, who was the member of the advisory subcommittee with the greatest knowledge of blood banking. From the outset he made it clear that the Red Cross was unconvinced about the efficacy of surrogate tests and believed that they would be costly in both money and

the loss of donors. The information he presented supported that position. Some of it was inaccurate. The Canadian Blood Committee and its advisory subcommittee did not attempt to evaluate or to supplement the information presented by the Red Cross. Nor did the members of the committee, each of whom was a senior employee of a provincial department or ministry of health, seek the advice of experts in their ministries about the nature and consequences of non-A, non-B hepatitis, as some had done with respect to the introduction of HIV-antibody testing.

The members of the Canadian Blood Committee had both the skills and the resources to conduct a cost-benefit analysis of surrogate testing. In December 1989, the secretariat of the committee estimated that it could cost the health care system nationally \$8.4 million per year to diagnose and begin the care of some 12,000 persons newly diagnosed as having acute post-transfusion non-A, non-B hepatitis. "Many millions of dollars more" would have to be spent on the subsequent treatment and hospital care of the estimated 3,200 of those persons who would develop chronic hepatitis, some of whom would develop cirrhosis and liver cancer. No attempt was made to estimate this additional cost of health care, nor the social and economic costs associated with the disease that would result if surrogate tests were not implemented.

The Canadian Hemophilia Society

Hepatitis had long been considered an acceptable risk of treating hemophilia, compared to the disabling and sometimes life-threatening bleeding episodes. The introduction of factor concentrates in the late 1970s transformed that risk from a probability to a near certainty, so much so that the first factor concentrates distributed by the Red Cross in Canada were labelled with the warning that "the presence of hepatitis virus should be assumed." In most cases, however, hepatitis was marked by relatively mild, flu-like illness and sometimes jaundice, and serious complications usually did not manifest themselves for ten or twenty years. Factor concentrates made it possible for severe hemophiliacs to treat themselves for the first time at home and enjoy near-normal lives. During the 1970s, the Canadian Hemophilia Society and its medical and scientific advisory committee sought to ensure that factor concentrates would be available to all hemophiliacs in Canada free of charge. However, many physicians with hemophiliac patients treated those who had never or seldom been exposed to factor concentrates with cryoprecipitate, which carried a lower risk of hepatitis, for as long as possible.

As the increased incidence of hepatitis among hemophiliacs became apparent in the late 1970s and early 1980s, the Canadian Hemophilia Society and its medical and scientific advisory committee endeavoured to make the hepatitis B vaccine available to those hemophiliacs who had not already developed hepatitis. Neither a vaccine nor a specific test existed for non-A,

non-B hepatitis. During the late 1970s and early 1980s, some manufacturers began to develop factor concentrates that were heat treated to inactivate the hepatitis virus. These early heat-treated concentrates were considered expensive and unproven, particularly against non-A, non-B hepatitis. Only in 1984 when the heat treatment of concentrates was found to be effective in inactivating HIV did they become widely accepted.

By the spring of 1987, some lay members of the Canadian Hemophilia Society began to demand the surrogate testing of plasma used to manufacture blood products. Although there was no consensus in the society's medical and scientific advisory committee about this issue, it asked the Canadian Blood Committee, through its advisory subcommittee, to establish an ad hoc committee to consider the question. The suggestion was not adopted by the Canadian Blood Committee. By February 1988, when the Canadian Hemophilia Society's medical and scientific advisory committee held its own conference, the issue of surrogate testing for blood products had become less urgent. It was clear by that time that all factor concentrates distributed in Canada would soon be wet heat-treated, a process shown to be effective in inactivating the causative agent or agents of non-A, non-B hepatitis. Even before this conversion to wet heat-treated products took place, some physicians who treated hemophiliacs used the emergency drug release program and clinical trials to ensure that hemophiliacs who would most benefit from wet heat-treated products received them before they were distributed nationally. Hepatitis was no longer considered by hemophiliacs and their physicians to be an acceptable and unavoidable risk of hemophilia treatment.

Surrogate testing outside North America

In their submissions, the Government of Canada and the Red Cross said that surrogate testing of blood donations for non-A, non-B hepatitis was not implemented in all western industrialized nations, and relied on this fact to support the reasonableness of the decision not to implement surrogate testing in Canada. It is correct that the surrogate tests were controversial in parts of the world other than North America, and that it was decided not to implement them in some countries.

The United Kingdom has been referred to as an example of an industrialized country that did not implement surrogate tests. The incidence of non-A, non-B hepatitis was much lower in the United Kingdom than in Canada and the United States, however. One study found it to be 2.5 per cent among cardiac patients who had received multiple units in transfusion, but the average rate was believed to be less than 1 per cent – so low that British blood bankers questioned whether it was cost-effective to implement even anti-HCV testing when it became available. The low incidence and the need for a randomized study were given as reasons for not adopting surrogate testing.

In Australia, where surrogate testing was not conducted routinely, the incidence was reported to be 1.6 per cent in a study published in 1982. Nevertheless, some Australian blood centres conducted one or both of the surrogate tests voluntarily. In general, countries in which the incidence of post-transfusion non-A, non-B hepatitis was low were most likely to decide not to implement surrogate tests routinely.

Countries with a significant incidence were more likely to introduce at least one of the surrogate tests. In France, for example, incidences of post-transfusion non-A, non-B hepatitis were found in different studies to be 4.4 and 26.5 per cent in Toulouse, 6.6 and 13 per cent in Paris, 8.1 per cent in Lyons, and 6.3 per cent in Nancy. In June 1986, the national advisory commission on blood transfusion, which advised the French Ministry of Health, asked members of the viral hepatitis working group of the National Society of Blood Transfusion to examine the problem of post-transfusion hepatitis and to propose methods of reducing it. The working group reviewed the French and international data on the incidence of post-transfusion non-A, non-B hepatitis in recipients of blood components and blood products, the consequences of the chronic disease, and the efficacy of surrogate testing. The working group noted that, although the studies conducted in France involved relatively small sample sizes, their results were generally consistent with those of the TTV study in the United States which, although not a randomized study, had the largest sample of donors and recipients. It also examined the feasibility of conducting surrogate tests in France and conducted a cost-benefit analysis of testing. In April 1987, it recommended the implementation of both ALT and anti-HBc testing. The group's full report, submitted in July 1987, gave detailed reasons for the recommendations, which were adopted by the Ministry of Health. ALT testing was implemented routinely throughout France in April 1988, and anti-HBc testing, in October 1988.

Events in France affected developments in Canada. Several studies of the efficacy of surrogate tests conducted by researchers in France demonstrated their usefulness. One of these studies, the Lyons study, was a randomized controlled study of the efficacy of ALT testing – the very kind of study that the Canadian Red Cross said was needed to justify the implementation of surrogate testing. The Lyons study showed that the incidence of non-A, non-B hepatitis was 6.25 per cent in recipients of the unscreened blood and 0.9 per cent in recipients of tested blood. When these data led to a decision to implement surrogate testing in France, pressure was increased on the Canadian Red Cross to implement these tests in Canada. Dr Perrault said at the time that, because of the events in France, Canada would have no choice but to implement surrogate testing.

Most European countries that conducted routine surrogate testing used only ALT tests. The use of anti-HBc as a surrogate test was difficult in countries with a high prevalence of hepatitis B because so many persons would react positively that the blood supply would be seriously depleted. Two such

countries were Italy, where one study detected anti-HBc in 44 per cent of blood donors, and Spain, where another study found anti-HBc in 14 per cent of donors. For such countries ALT testing was preferable, although even with ALT testing the incidence of post-transfusion non-A, non-B hepatitis remained high. The difficulty in using anti-HBc in countries with a high prevalence of hepatitis B infection was recognized by the World Health Organization which, in its 1990 consensus statement on screening of blood donation, stated that "the usefulness of surrogate tests ... should be evaluated in different populations, but tests for antibody to hepatitis B core antigen (anti-HBc) are not applicable in areas of high HBV endemicity."

German blood centres began the ALT testing of donations as early as 1968. In July 1985 ALT testing was required of all plasma used in the manufacture of imported blood products. Germany did not require anti-HBc testing, but its efficacy was demonstrated in at least one study and some blood centres conducted anti-HBc testing voluntarily. ALT testing was also required by regulation or conducted routinely in Japan, Switzerland, Spain, Italy, Portugal, Finland, and Malta. In addition, ALT testing was conducted voluntarily by some blood centres in Australia, Belgium, and Luxembourg.

Conclusion

Until the advent of AIDS, blood bankers had come to view the transmission of infectious diseases by transfusion, like hepatitis B, with a certain complacency. The decision to implement surrogate testing in the United States signified that blood bankers in that country had learned a valuable lesson: that appropriate and prudent decisions about matters of significant and far-reaching public health consequences must sometimes be made on the basis of existing evidence. Subsequent studies proved that the decision was correct. Even after the introduction of HIV-antibody testing, the introduction of either or both of the surrogate tests significantly reduced the incidence of post-transfusion non-A, non-B hepatitis.

The effect of the failure to implement surrogate testing in Canada is illustrated by the Blajchman-Feinman study itself, which confirmed that surrogate testing would have significantly reduced the incidence of post-transfusion hepatitis. The results of the study, published in *The Lancet* in 1995, support the conclusion that the implementation of both surrogate tests would have reduced the incidence of post-transfusion hepatitis by 75 per cent, and the incidence of post-transfusion hepatitis C by 85 per cent, in the period before the introduction of HCV-antibody testing in Canada. The decision of the Red Cross not to implement anti-HBc and ALT testing of blood donations in Canada as surrogates for non-A, non-B hepatitis was not an acceptable one.

The Consequences of the Contamination of the Blood Supply

It is impossible to determine precisely how many Canadians were infected, during the 1980s, with the causative agents of AIDS and hepatitis C through contaminated blood, blood components, and blood products. The best we can do is to estimate the numbers so infected from what we do know. The numbers that follow are of the persons directly infected through transfusion or the use of blood products. Others were secondarily infected through sexual contact with those persons infected through transfusions and the use of blood products.

The transmission of HIV through transfusion

The most reliable studies of transfusion-associated infection with HIV in Canada have been carried out by Dr Robert S. Remis, an epidemiologist, formerly the director of the regional bureau of infectious diseases in Montreal and now a consulting epidemiologist with the AIDS bureau of the Ministry of Health of Ontario and an associate professor in the Faculty of Medicine at the University of Toronto. In 1994, Dr Remis undertook a study, supported by the Laboratory Centre for Disease Control, that had, as one of its objectives, "[t]o estimate the number of HIV infections among persons transfused in Canada from 1979–1985, the number of HIV-infected persons still alive and unidentified and the expected prevalence of HIV infection among transfused persons." In his analysis he drew on three databases: the national surveillance program for AIDS, in which the Laboratory Centre for Disease Control collected and analysed the cases of AIDS reported to it by provincial public health authorities; information about applicants to the Extraordinary Assistance Program, under which the federal government compensated persons who were infected with HIV through blood components or blood products; and information from trace-back investigations conducted by the Canadian Red Cross Society (Red Cross) to identify the donors of blood that had been identified as contaminated.

It is unnecessary to review in detail all the factors Dr Remis took into account in his analysis, including the underreporting of the disease or the methods used to validate his estimates. His results are summarized in Table 26.1. It must be emphasized that the numbers in the table and in what follows are estimates, based on partial data and subject in every instance to some uncertainty. They are, nevertheless, the result of a careful and detailed analysis. They give the most reliable estimate available of the effects of HIV contamination of the blood and blood components used in transfusions in Canada, from the emergence of AIDS until the introduction of testing for HIV antibody.

Dr Remis estimated the number of persons infected with HIV through blood transfusions from 1978 to 1985. The number increased in every year after 1978 until it reached a cumulative total of 1,148 persons in 1985. In November 1985, the Red Cross began testing all blood donations for the presence of HIV antibody. A small but undetermined number of additional

Table 26.1
Cumulative number of HIV and AIDS cases from transfusion, 1978–85

Year	Cumulative HIV infections	Mortality		Infected Survivors	
		Early*	Late†	With AIDS	AIDS free
1978	13	5	0	0	8
1979	25	10	0	0	14
1980	50	22	0	1	28
1981	110	47	0	2	61
1982	255	108	0	5	141
1983	470	203	1	12	255
1984	770	337	2	25	407
1985	1,148	509	3	46	589
1986		541	7	80	521
1987		554	13	117	464
1988		564	22	154	409
1989			32	187	366
1990			41	216	327
1991			51	240	294
1992			57	259	269
1993			63	274	247

* Early mortality = death in the first three years after a transfusion.

† Late mortality = death more than three years after a transfusion.

Source: Based on R.S. Remis and R.W.H. Palmer, "The Epidemiology of Transfusion-Associated HIV Infection in Canada, 1978–1985" (unpublished, 1994).

transfusion-associated AIDS cases have occurred since the introduction of the test because, although highly sensitive, the test is not infallible. Dr Remis estimated that, during 1985, 378 persons were infected, approximately one-third of the total; the year before, 300 persons were infected. Approximately 70 per cent of transfusion-associated infections occurred from blood that was processed by the Red Cross's Toronto, Montreal, and Vancouver centres; this percentage reflects both a higher prevalence of HIV infection in blood donated in those cities and the greater volume of blood distributed by those centres.

Approximately 50 per cent (564) of those infected by 1985 (1,148) died within three years of receiving a transfusion, most of them from the conditions that had necessitated the transfusions. By the end of 1993, an additional 5.5 per cent (63) died after surviving for more than three years, some of them from AIDS. Of those persons still alive at the end of 1993, he estimated that 274 had developed AIDS, and another 247 were infected with HIV but did not yet have AIDS. Dr Remis estimated that approximately 100 of those persons who were still AIDS free were not yet known and might be unaware of their infection. This estimate was consistent with a study conducted in early 1993 at the Hospital for Sick Children in Toronto that found seventeen patients infected with HIV, of whom six were unaware of their condition.

The spread of HIV among hemophiliacs

The spread of HIV and AIDS among Canadian hemophiliacs can be traced primarily through two major research projects conducted under the leadership of Dr Christos Tsoukas, a member of the division of clinical immunology and allergy of the Montreal General Hospital and the director of the hospital's immune deficiency treatment centre. The first, a study of severe hemophiliacs in Montreal (the Montreal study), began in 1982; the second, a broader nationwide study, began two years later. Much of his research has inevitably been historical reconstruction, because the spread of the infection could not be measured precisely until the virus had been discovered and a test for HIV antibody had become readily available. It was only then that analysis of stored specimens of serum, including those of the patients enrolled in Dr Tsoukas's Montreal study, disclosed the extent to which HIV had spread among Canadian hemophiliacs, even before 1982.

In early September 1982, when he was a resident at the Montreal General Hospital, Dr Tsoukas began the first study of immune deficiency among Canadian hemophiliacs. With the assistance of Dr Hanna Strawczynski, then the director of the hemophilia treatment program at the Montreal Children's Hospital, he enlisted thirty-four patients with severe type A hemophilia, each of whom used more than 40,000 units of factor VIII concentrate annually. Dr Tsoukas has followed this original group, or its survivors, ever since.

In April 1983, Dr Tsoukas and his colleagues sought financial support for a three-year study (the multicentre study) to be conducted in cooperation with hemophilia centres throughout Canada. The Medical Research Council agreed to fund the study in the autumn of 1983 and, after some delay caused largely by logistical and technical difficulties, the project began in August 1984. Its primary objectives were to assess the incidence and prevalence of immune system abnormalities among hemophiliacs, to study the relationship between these abnormalities and the use of particular blood products, and to determine the relationship between changes in the immune function of hemophiliacs and the development of AIDS. The study included the collection of tissue and serum samples, which were analysed for deficiencies in the immune response function and, eventually, for the presence of the causative agent of AIDS. The study was expected to run to September 1987, but the Medical Research Council funding continued until January 1988, and most subjects were monitored clinically and immunologically until 1991. Eleven centres in nine provinces participated. In total, 372 persons with bleeding disorders were involved.

The multicentre study demonstrated a direct relationship between the type and quantity of coagulant blood products used and the probability of testing positive for HIV antibody. Among persons with type A hemophilia who had used only cryoprecipitate, the proportion that tested positive was 9 per cent; among those who had used both cryoprecipitate and factor concentrates, it was 50 per cent; among those who had regularly used concentrates, it was 84 per cent. Only two of the forty-one type B hemophiliacs who had used factor IX concentrate tested positive. Of the forty-two who had von Willebrand's disease, only twenty-six used plasma derivatives (primarily cryoprecipitate), six of whom were HIV-antibody positive.

Of the 372 persons in the study, 193 (52 per cent) were HIV positive. Almost all the infected persons seroconverted before the introduction of heat-treated factor concentrates in the summer of 1985. The persons in the study were not randomly selected, but were a representative sample of Canadians with bleeding disorders who used factor replacement products. Approximately one of every six or seven persons who used those products was a subject in the study. It is not unreasonable to infer from the study that approximately half the persons in Canada who used factor replacement therapy became infected with HIV.

There was a strong association between exposure to non-heat-treated concentrates and the risk of HIV infection. Among severe type A hemophiliacs (the group that consumed the greatest amount of factor VIII concentrate), 159 had used non-heat-treated concentrate, and 91 per cent of them tested positive. Of the thirty-two severe type A hemophiliacs who remained negative, half had never used non-heat-treated factor VIII concentrate, and a further six had been treated with cryoprecipitate as well as with concentrate.

Calgary was the only city in the study where the rate of HIV infection was significantly lower than the national average. There, only 20 per cent of the persons in the study were infected with HIV. The rate was low because many persons with bleeding disorders who were treated in Calgary used cryoprecipitate and fresh frozen plasma instead of factor concentrates.

It is only from Dr Tsoukas's original group of thirty-four patients in Montreal that we can calculate the speed with which HIV infection and AIDS spread among Canadian hemophiliacs. The serum samples of these patients had been frozen and stored from the start of the study in the autumn of 1982. As was later learned, 60 per cent were already HIV positive at that time. By 1984, only one of the group remained negative. Initially, they were all free from the signs and symptoms of AIDS. By June 1987, 90 per cent showed clinical signs of infection and 38 per cent had AIDS or AIDS-related symptoms. One had already died, two were critically ill, and five had developed life-threatening conditions. A year later, three of the original group had died of AIDS, and 52 per cent had AIDS or AIDS-related symptoms. By May 1993, the number of deaths had reached fifteen. The one patient of the original thirty-four who had been reported uninfected in 1984 was still negative for HIV antibody.

The number of subjects involved in the Montreal cohort was too small to permit reliable extrapolation at the national level. However, Dr Tsoukas's findings with respect to his Montreal patients are consistent with the results of the Multicentre Hemophilia Cohort Study of HIV infection among more than 600 hemophiliacs seen at five treatment centres in the eastern United States between 1982 and 1990. As with the Montreal study, plasma and serum samples from persons enrolled in the U.S. study were coded, frozen, and shipped to a central laboratory even before HIV testing was available. In the group with hemophilia A, the proportion that was HIV-antibody positive was almost 100 per cent among those who used high or moderate doses of factor VIII concentrate, 56 per cent among those who received low doses, and 16 per cent among those who used only cryoprecipitate. The researchers found that the risk of exposure to HIV among high-dose users of factor VIII concentrate was high before 1980, and peaked at the end of 1982. At one of the five U.S. hemophilia treatment centres studied, 50 per cent of the high-dose users were already HIV positive by July 1980. The researchers estimated that, by January 1983, between 62 per cent and 89 per cent of all U.S. hemophiliacs who had been infused with factor VIII concentrate, regardless of dosage, and who eventually tested positive, had already been infected.

Given the substantial dependence of Canadian hemophiliacs on commercial factor concentrates produced by U.S. manufacturers, and the similarity of results from the Canadian and U.S. studies, it is reasonable to assume that the results of the U.S. study are representative of the Canadian experience. The strong inference to be drawn from the studies is that, in Canada, the vast majority of the severe type A hemophiliacs who became HIV positive

were infected before heat-treated factor concentrates became available in the summer of 1985. The small but significant exception to the high rate of seroconversion among severe type A hemophiliacs consisted of most, but not all, of those type A patients for whom cryoprecipitate remained the factor replacement therapy of choice.

The transmission of hepatitis by transfusion

The media commonly report that more than 12,000 persons have been infected with HCV, the virus that causes hepatitis C, through the blood supply. The source of that number, as well as the time period to which it relates, is uncertain. No study similar to Dr Remis's has been conducted of the number of persons who acquired hepatitis C through blood transfusions in Canada during the 1980s.

The Laboratory Centre for Disease Control has used data from two sources – the Toronto incidence study conducted by Dr Victor Feinman from 1983 to 1985; and the multicentre study of the efficacy of surrogate testing for non-A, non-B hepatitis in Toronto, Hamilton, and Winnipeg conducted by Dr Morris Blajchman and Dr Feinman between 1988 and 1992 – to estimate the number of persons infected with HCV in Canada from mid-1986 (when surrogate testing was introduced in the United States) to mid-1990 (when HCV-antibody testing was first implemented in Canada). In an affidavit filed in a proceeding in the Supreme Court of British Columbia in February 1997, Dr Paul Gully, then the chief of the Blood-borne Pathogens Division of the Laboratory Centre for Disease Control, estimated that approximately 28,600 persons may have contracted HCV through blood transfusion in Canada from mid-1986 to mid-1990. This estimate was based on the assumption that 2.2 per cent of transfusion recipients in Canada were infected with HCV during this period. This incidence represents the mid-point between the incidence of post-transfusion hepatitis C as shown by an analysis of blood samples collected by the Toronto study between 1983 and 1985, and by the Blajchman–Feinman multicentre study between 1988 and 1990. The calculation also assumed that there were an estimated 1.3 million transfusion recipients in Canada during the four years.

I accept Dr Gully's conclusion that in the period 1986 to 1990, approximately 28,600 persons might have been infected by HCV through blood transfusion. This estimate was calculated for the purpose of litigation about the transmission of post-transfusion HCV in British Columbia for the period mid-1986 to mid-1990. Accordingly, no attempt was made to estimate the number of persons who developed post-transfusion hepatitis C before mid-1986 or after mid-1990 to mid-1992, when the second-generation antibody test was introduced, or to estimate the number of persons who might have developed other types of post-transfusion hepatitis throughout the 1980s.

It stands to reason that the number of cases of post-transfusion hepatitis C occurring between 1980 and 1986 was even higher because the rate of post-transfusion hepatitis C declined after the introduction of HIV testing in November 1985. Even when the rate of post-transfusion HCV was further reduced in 1990 by the implementation of the first generation of HCV-antibody testing, there continued to be a significant number of cases of post-transfusion hepatitis C until mid-1992.

The transmission of hepatitis by blood products

Although the number of persons infected with hepatitis C through blood transfusions is far from clear, the number of hemophiliacs infected through the use of blood products is more certain. In 1992, the Canadian hemophilia clinic directors group conducted a study of 884 hemophiliacs, approximately half the total number of hemophiliacs listed in the national registry. The persons in the study reflected in general the total Canadian hemophiliac population with respect to both the type and the severity of the condition, although severe hemophiliacs were slightly overrepresented. Because the study was conducted in 1992, it did not include many hemophiliacs who had already died of HIV-related causes, and who may or may not have been HCV-antibody positive.

Of the 884 persons in the study, 560 (64 per cent) reacted positively to second-generation tests for HCV antibodies. Among persons with severe type A hemophilia, the incidence of hepatitis C was 70.4 per cent; among moderate type A hemophiliacs, it was 66.1 per cent; and among mild type A hemophiliacs, it was 47.6 per cent. The comparable figures for persons with type B hemophilia were 83.6 per cent, 61.8 per cent, and 35.7 per cent, respectively. The incidence of hepatitis C was significantly higher among hemophiliacs who had been treated with factor concentrates than among those who had been treated only with products derived from a single donor, such as cryoprecipitate and fresh frozen plasma; the incidences were 69 per cent and 36 per cent, respectively. None of the hemophiliacs who had been treated exclusively with wet heat-treated factor concentrates was HCV-antibody positive.

Although the clinical consequences of HCV infection may be less serious than those of HIV, they result in serious illness and death in a significant number of cases. Research conducted in the United States shows that the rate of persons with hemophilia type A who died from liver disease remained relatively constant at approximately 13 per cent throughout the 1980s.

The consequences of contamination

Statistics are impersonal and abstract. More than 180 persons infected with HIV and hepatitis through the blood supply, or members of their families, testified at the Inquiry about what the contamination of the blood supply has

meant to them. They came from all provinces and were infected at various times – in the womb, and in childhood, adolescence, middle age, and later life. Some infected persons were represented by family members because they were too ill to testify, or because the infected persons had already died.

Many witnesses said they had not been told before an operation that a blood transfusion might be necessary, or told afterwards that one had been administered. Some did not learn they were infected until they had developed indications of AIDS or signs and symptoms of chronic liver disease. Others, particularly those with HIV, did not learn they were infected until they underwent a routine medical examination for life insurance. Their testimony was consistent with a survey conducted during the Inquiry that found that only 10 per cent of the hospitals in Canada had a written policy requiring that their patients be informed of the risks of a blood transfusion, and that most hospitals did not mention blood or blood products on the consent forms their patients were asked to sign before surgery or anesthesia. Other witnesses said they had been inadequately counselled about the risks of exposure to hepatitis C or HIV infection through a blood transfusion or blood products. Some witnesses said they had not been told of the dangers of using blood products, or were given no choice in the blood products administered to them.

It is impossible to record all their testimony here. Many witnesses expressed a sense of betrayal by the blood system they had implicitly trusted. Their experiences and perceptions are fairly represented by the following summaries of the testimony of seven of the witnesses.

- A fifty-five-year-old patient did not consent to the administration of blood before elective surgery in 1983. His physician did not discuss with him the risks associated with a blood transfusion or discuss the possibility of depositing units of his own blood before the operation. Nor was he told after the operation that he had been given two units of red blood cells. That information did not appear on his discharge summary, nor was his family physician told of it. Ten years after his surgery, he learned that he had received a contaminated blood transfusion and that he was infected with HIV. By that time, he had transmitted the virus to his wife. He questioned whether the blood transfusion was necessary because his medical chart recorded that “blood loss was negligible.”
- A premature infant was transfused with 16 cc, a tablespoon, of red blood cells in 1985 within three weeks of his birth. The attending physicians did not obtain the consent of the parents to the transfusion, nor did they tell them of it afterwards. The child became very ill in 1992. He had swollen glands, a high fever, and an unrelenting cough. In 1993, in a radio broadcast, the boy’s mother heard that former pediatric cardiac patients should be tested for the presence of HIV antibody. The parents decided to have their son tested. Had they had any reason to decide to do so earlier, the

child could have received treatment that might have prolonged his life. The boy developed AIDS. When they testified, the parents still had not been told the reason why the “topper up” blood cells were given.

- A hemophiliac testified that he switched from cryoprecipitate to factor VIII concentrate in the late 1970s. From 1981 to 1986, he obtained his medication through a repeatable prescription at a hospital blood bank. He was not told that HIV could be transmitted in blood products. He said he was on concentrate only “because of convenience” and had never experienced life-threatening bleeding; had he known that HIV or other diseases could be transmitted through concentrates, he would either have refused to accept any treatment for his blood disorder or he would have returned to the safer form of treatment with cryoprecipitate. After he learned he was HIV positive, his wife was tested for the presence of HIV antibody and her results were negative. He was told by his physicians that hemophiliacs infected with HIV were unlikely to transmit the virus to their sexual partners, and that it was unlikely that HIV-positive hemophiliacs would develop AIDS. Despite practising safer sex, his wife tested HIV-antibody positive a few years later. He died of AIDS shortly after testifying at the Inquiry.
- A middle-aged man received a blood transfusion during cardiac surgery in December 1984. In April 1989, the head of the hospital blood bank told the man’s physician that his patient had received potentially HIV-contaminated blood. The physician decided not to inform his patient of the possible infection. He assumed his patient no longer engaged in sexual relations with his wife, and he was concerned that the information could jeopardize his patient’s mental health and cardiac condition. In late 1989, the patient had flu-like symptoms. In March 1990, he had seizures and developed pneumonia. He was admitted to hospital, where he died two and a half weeks later. In a telephone call the next month, the physician told the wife that her husband had tested HIV-antibody positive. She had herself tested, and learned she had contracted the virus. She later died of AIDS.
- A woman testified about the death of her son, a mild hemophiliac, who had been treated exclusively with cryoprecipitate before 1979. From 1979 to 1984, he did not use any blood products. In March 1983, the medical and scientific advisory committee of the Canadian Hemophilia Society recommended that cryoprecipitate rather than factor concentrates be used to treat patients with classic hemophilia who had never used concentrates. Her son fit this category, but was treated in a local hospital one year later with factor concentrates. The hospital ignored requests from the hemophilia clinic and the family that the child be treated with cryoprecipitate. The boy experienced bleeding in 1984 and, on each occasion, was treated with concentrates. In 1985, he tested positive for HIV and hepatitis C. He died in February 1993.

- In November 1989, a forty-year-old woman underwent dental surgery as an outpatient in a hospital. Because she had a bleeding disorder, she was given a platelet transfusion. Some time later she began to experience nausea, weight loss, and severe headaches. She developed jaundice, and was admitted to the hospital in January 1990. She was diagnosed with hepatitis C and told she would likely develop cirrhosis of the liver.
- In July 1989, a young man was in a motorcycle accident. After he had spent several days in the hospital, he was given several units of blood "as a precautionary measure" because he had lost blood in the accident. Several months after he was released from the hospital, he began suffering from extreme fatigue. He was readmitted to the hospital in December 1989 and a liver biopsy was performed. He was told that he had cirrhosis of the liver and had contracted non-A, non-B hepatitis. One year later, his doctor told him that he had hepatitis C and that he would certainly develop liver cancer within the next ten years.

Diseases transmitted through the blood supply have not only cost lives but have imposed significant financial strains on those infected and on their families. Treatment is expensive. Several witnesses infected with HIV and hepatitis C were no longer able to work; some were not eligible for disability or life insurance. Some witnesses were about to lose their homes. Some had moved to subsidized housing or had had to resort to social assistance.

Infection has also carried with it discrimination and alienation in many forms. An HIV-infected child was forced to leave his school after neighbours petitioned that he be expelled; obscene words were spray-painted on his house, the tires on his mother's car were slashed, and he was ostracized at a health club. A hemophiliac said his colleagues at work refused to share the bathroom with him and that his six-year-old daughter had found a sign on their lawn that said her father was "queer" because he had AIDS. A woman infected with HIV through a blood transfusion said that family members shunned her and were convinced that if she touched or breathed on them, they could be infected; when she was transported to hospital in 1989, the ambulance driver recommended that her "infected clothes" be burned. Her physician would not treat her for a rash for fear he would contract HIV. Some patients with HIV were refused dental care. Many persons justifiably feared that disclosure of their HIV status would result in discrimination. A father said that his adult hemophiliac son, who was HIV positive, refused to disclose his illness out of fear of losing his job and, as a result, could not recover the cost of his medication from the company's health insurance plan. A husband said he feared he would lose his job if his wife's HIV infection were known at work.

In a letter to the premier of his province, a severe hemophiliac infected with hepatitis C and HIV through blood products described the isolation and stigmatization of persons infected with these diseases. His letter reads, in part:

Some of us were so frightened and confused that we did not even kiss, hug or touch our children for 3 years for fear of contaminating them. As a father you can, I hope, understand the torment and anguish you would feel if you caused your own child's death. We not only understood this reality but lived daily with it ...

As a man, I hope you can appreciate and understand the necessity of responding to your sexual desires. But do you fully appreciate what it does to a person to lie each night for five or more years with the woman you love, the mother of your children, and be mortally afraid to touch her for fear that both of you will die of AIDS and that as a direct result of your actions your wife will die and your children will be both motherless and fatherless? Safe sex works well in individual situations but over a long period of time the percentages work against you ...

I once had a loving wife and 4 children, a successful business career and a lovely home ... My health deteriorated, and 3 years ago I had to quit a \$50,000 a year job ... My marriage is in ruins, I now live [apart from] my wife and children ... Hemophiliacs in general, before AIDS, had a very stable marriage, very few resulted in divorce or separation, now this situation has reversed and we face one of the highest per capita separation and divorce rates. The irony of this situation is, when we desperately need a stable, a loving relationship to fight the stress of AIDS – we are denied it.

